

[Discussions] Vol. 17 Iss. 2

Follow this and additional works at: <https://commons.case.edu/discussions>

Recommended Citation

() "[Discussions] Vol. 17 Iss. 2," *Discussions*: Vol. 17: Iss. 2, Article 4.

DOI: <https://doi.org/10.28953/2997-2582.1181>

Available at: <https://commons.case.edu/discussions/vol17/iss2/4>

This Article is brought to you for free and open access by the Undergraduate Research Office at Scholarly Commons @ Case Western Reserve University. It has been accepted for inclusion in Discussions by an authorized editor of Scholarly Commons @ Case Western Reserve University. For more information, please contact digitalcommons@case.edu.

Discussions

The Undergraduate Research Journal of CWRU

VOLUME XVII, ISSUE II



DISCUSSIONS

Undergraduate Research Journal of CWRU

Table of Contents

Interview

Faculty Spotlight: Dr. Harsh Mathur

4

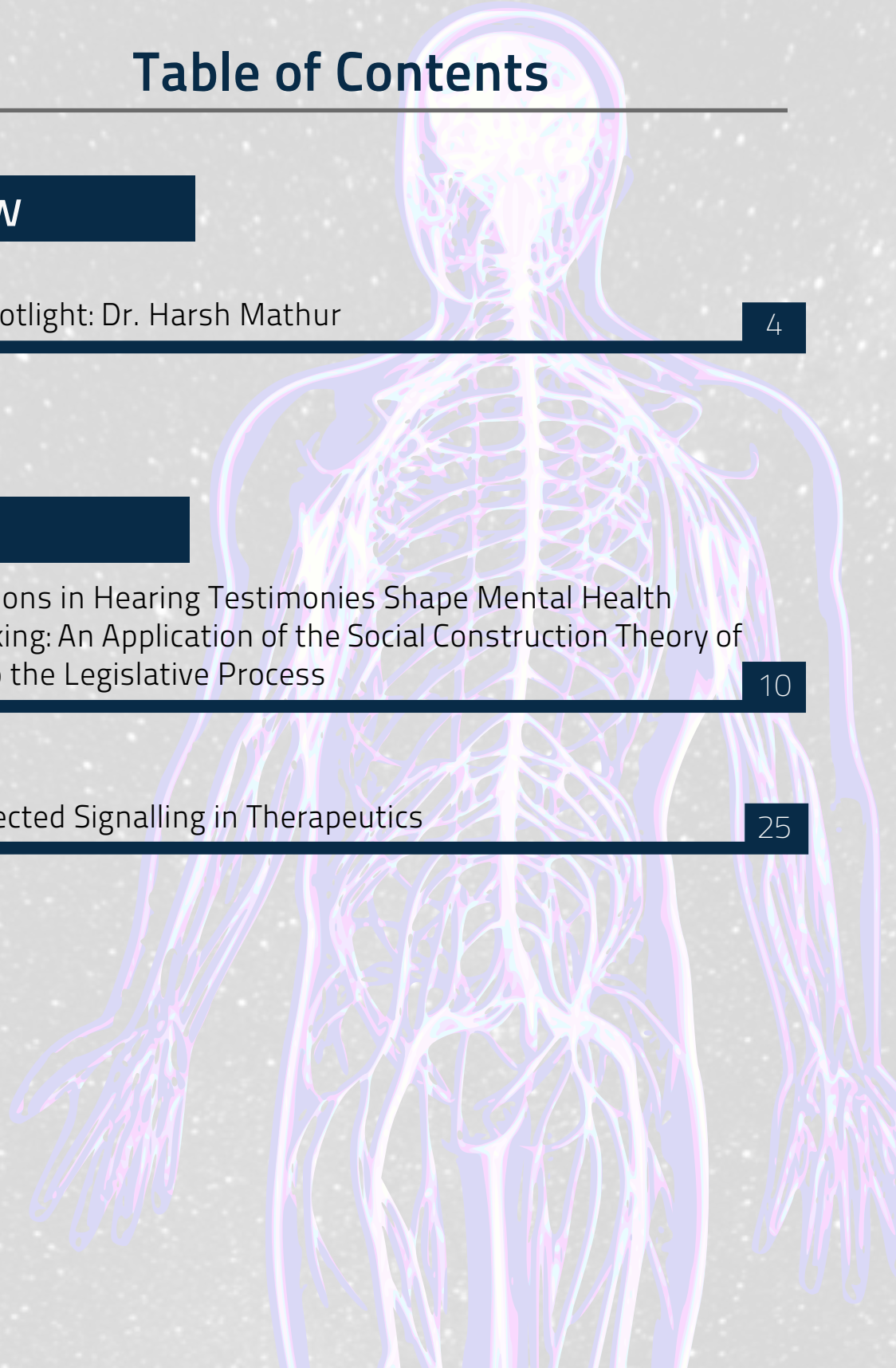
Review

How Emotions in Hearing Testimonies Shape Mental Health Policy-Making: An Application of the Social Construction Theory of Emotion to the Legislative Process

10

Ligand Directed Signalling in Therapeutics

25

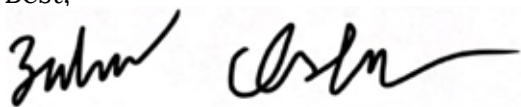


Letter from the Editor

Dear Reader,

Thank you for deciding to read this issue of Discussions: The Undergraduate Research Journal of CWRU. I am pleased to present you with our 2021 issue, and given the circumstances we found ourselves this year, I could not be more proud of our staff's dedication to bringing you the best of undergraduate research despite the times. Discussions strives to bring quality research from around the country and world to our audiences. In this 2021 edition, we feature articles about emotions in testimonies, and ligand signaling, an interview with an esteemed CWRU physics professor, and so much more. We here at Discussions hope you enjoy the articles and interviews within this issue and come away having learned something new and engaging. An encouragement of undergraduate research is imperative to furthering interest in the arts and sciences so that we may build on the discoveries of today, tomorrow, and the future. Discussions seeks to participate in the goal by providing an outlet for students to publish and share their research. We are deeply grateful to the Support of Undergraduate Research and Creative Endeavors (SOURCE) office at Case Western for their ongoing guidance and support in our endeavors. Although Discussions is based at Case Western, we accept submissions from any other undergraduate institution. In fact, in the past we have had submissions from every inhabited continent. If you share Discussions' passion for celebrating excellent undergraduate research, consider submitting to the journal. We accept undergraduate research in all disciplines, and welcome submissions at any time. If you, or someone you know, would like to submit to Discussions, we encourage you to visit our website at www.case.edu/discussions for detailed instructions. If you are interested in participating further with the journal or have any other questions, you can email us at Discussions.Journal@gmail.com to learn more. I would also ask our readers to contribute to our growth by finding us on Facebook or Instagram to hear about submission deadlines and the release of new issues. As always, I would like to thank all of those who contributed to this issue of Discussions, including all our submitters, authors, the Editorial Board, and staff members. I would also like to thank the University Mediaboard for their unwavering support for our Publication. Finally, I thank you, our reader, for reading and joining our celebration of undergraduate research.

Best,



Zahin Islam
Editor-in-Chief

media board



Editorial Board

Editor-in-Chief
Zahin Islam

Managing Editor
Rebecca Wilcox

Assistant Director of Layout
Neel Agarwal

Assistant Director of Design
Grace Huang

Director of Content
Izzy Genuario

Assistant Director of Content
Natalie Zajczenko

Director of Review
Josh Freeze

Assistant Directors Of Review
Priyanka Agochiya
Aayushi Chechi

Director of Business
Gloria Liu

Assistant Director of Business
Madeleine Clore

Director of Public Relations
Akshaya Ramakrishnan

Director of Marketing
Anjali Raju

Director of Information
Nihal Minjila

Reviewers

Nikhita Arun, Adi Breitman, Andrew Chan, Aayushi Chechi, Zhanda Chen, Madeleine Clore, David Frost, Isabella Genuario, Mia George, Hannah Gold, Santosh Hanumanthu, Natalie Hoffner, Soorya Janakiraman, Bhavya Krishna, Hayley Latta, Nicholas Laurencelle, Gloria Liu, Adrian Palumbo, Anjali Raju, Tiffany Tsai, Kiley Urquhart, Alekhya Vadlakonda, Shejuti Wahed, Janet Wang, Benjamin Wellnitz, Jonathan Willcutt, Marlee Yancey, Natalie Zajczenko, Eric Zhang, Nobel Zhou

Copy Editors

Priyanka Agochiya, Nikhita Arun, Ansh Bhatia, Madeleine Clore, Grace Evans-Golden, Josh Freeze, Mia George, Hannah Gold, Grace Huang, Anjali Raju, Sofia Splawaska, Alekhya Vadlakonda, Evan Vesper, Rebecca Wilcox, Jon Willcutt, Eric Zhang

Designers

Nikhita Arun, Mia George, Aria Patel, Monisha Raju, Alekhya Vadlakonda

Advisors

Staff Advisor: Sheila Pedigo

Photographers

Neel Agarwal, Mia George, Aria Patel

Cover Design

Rebecca Wilcox

AN INTERVIEW WITH

Dr. Harsh Mathur

By Jonathan Wilcutt

A Selection of Dr. Mathur's Work

Mathur, H., Brown, K., & Lowenstein, A. (2017). An analysis of the LIGO discovery based on introductory physics. *American Journal of Physics*, 85(9), 676–682. <https://doi.org/10.1119/1.4985727>

Jones-Smith, K., & Mathur, H. (2006). Revisiting Pollock's drip paintings. *Nature*, 444(7119), E9–E10. <https://doi.org/10.1038/nature05398>

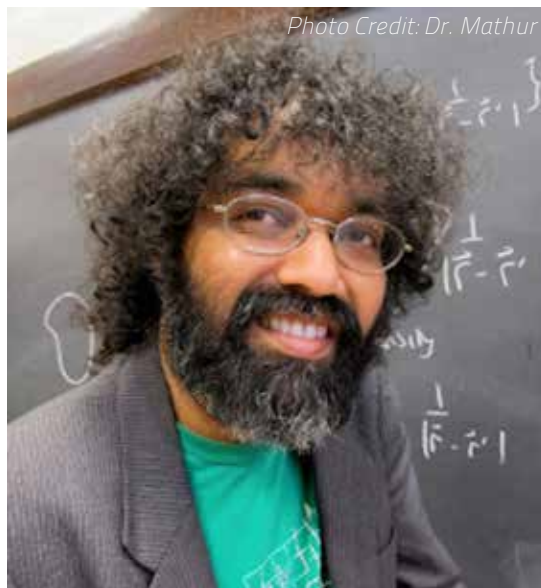
Dr. Harsh Mathur is a Professor in the Case Western Reserve University Physics Department. His current research interests include condensed matter theory, theoretical particle astrophysics, and cosmology. Dr. Mathur received his Ph.D. from Yale University. In this interview, he discusses his journey in the field of physics and the lessons he learned along the way.

This interview has been edited for length and clarity with Dr. Mathur's consent.

Q: What brought you to physics? How did someone with such broad interests settle into just one field?

A: What brought me into physics was astronomy initially. I realized that if I'm going to work in astronomy, I need to understand physics and math. And then once I got into physics, I discovered quantum physics and thought that was the coolest thing in the world. Quantum mechanics is buried deeply into subatomic structures.

Typically, we don't see quantum phenomena in everyday life. You and I are sitting here, and it's a very ordinary world. But deep down inside, the world is very strange. In condensed matter physics, we can access that strangeness, and it determines the properties of materials. This was absolutely fascinating, but I did have my interest in astronomy, fundamental physics, elementary particle physics, and cosmology lurking in the



background. I joined the faculty here in 1995. I was doing quantum condensed matter physics until around the 2000's, but then I got diverted into doing some other things because I shared the corridor.

"Once you start working with young people, you have to make more of a commitment...You have to become a card-carrying member of the community so that you can support their careers..."

My office is right next to the cosmologists, and we were always talking. Sometimes we would get into quite deep conversations. Whether you are doing quantum condensed matter physics or cosmology, many of the tools of science are more or less the same. But it was just the sort of thing we talked about over coffee, and then I would go back to my life and they would go back to theirs. But at some point, I wound up working with a postdoc and a student in their group whose advisor I became eventually. Once you start working with young people, you have to make more of a commitment. You can't just have an interesting conversation and leave it there. You publish papers. You have to become a card-carrying member of the community so that you can support their careers and so on.

It became real because I started working with the Postdoc and the student, and there's a bit of a story there—I actually migrated into cosmology by way of art history. We have the pizza seminar on Fridays where each week people get together—the students, the faculty, the postdocs—and alphabetically, more or less, people get to speak. That's the price you pay for the pizza. Usually people talk about their own research, cosmology, or some interesting new paper that they read on the arXiv so we can all stay up to date on interesting things that are happening in the field.

My student, Kate Brown, decided when it was her turn, she'd heard far too many talks about the cosmic microwave background and it might be fun to do something else. So she went scouting around and she found a Nature article that claimed that the paintings of Jackson Pollock were fractal and that you could use fractal analysis to tell if they were authentic. So she decided that would be a fun thing to present.

But in the course of preparing the presentation, she realized it didn't make any sense at all. She instead presented a really hilarious critique of the paper. I was quite impressed because Nature is a prestigious journal, and for a beginning graduate student to have the confidence to decide something in the journal is wrong and then put up really good reasons why impressed me. I and other people told her that she should write it up. She didn't because students never do what you tell them. She thought that she had to work in cosmology and be writing papers in that area if she was to have any future in this field.

But then six months later, there was front page news in The New York Times that a cache of paintings had been found that belonged to a guy named Alex Matter. His parents were friends of Pollock. Matter found these 25 paintings in his basement with a note from his dad saying the paintings were by Pollock. The art history world got divided about it, whether they were really by Pollock or not, or whether they were just student paintings of some sort. Scientists claimed that they had done fractal analysis and demonstrated these things weren't Pollock.

At that point, Kate agreed that we did need to write a paper debunking it. My favorite part of the paper was when she performed fractal analysis on this really childish drawing of stars that she made. According to the test from the paper, it was an authentic Pollock. This got to be a big media story. It got into hundreds of newspapers around the world. What we used to tell the newspapers was that, "either their test is wrong or our drawing is worth \$140,000,000, and we're happy with either outcome." It wound up being in a textbook on chaos theory, the New York Times, and Nature. Not so bad for a student's first project.

Q: Already you've mentioned that some of your biggest career moments have happened because of coffee and conversations. How do connections with the community drive innovation?

A: Physics as a whole is a very collaborative field. It is not the case that you just sit in some dungeon by yourself doing some calculations, although there are times when you have to hide away and do that, but a lot of it is collaborative and discussion based. The best ideas come that way. Whole programs get created that way. My story is actually very typical for people like me who do theoretical physics and mathematical physics, mostly pencil and paper calculations.

Q: How big of a separation in Physics and other quantitative fields is there between computer simulations, analytical results, and experimentation? How intertwined are these all?

A: We only do simple computations on our computers and the rest by hand. The philosophy here is one described by a great mathematical physicist Eugene Wigner. Wigner used to say if someone did purely computer analysis that, "I'm glad your computer understands the problem, but I would like to understand it too." I think that's an old-fashioned attitude that we have to shed. To refer to today's Nobel Prize [in climate models and spin glass], I think advances in climate science would not be possible without computers. It's simply not possible to work these things out by hand. But I think all of these things are

complimentary. Computers haven't displaced the need for traditional pencil and paper methods, but rather they've augmented it in a very powerful way. Even the purest of pencil and paper theorists can't avoid some computing, but basically if I can't run it on my Macbook, I don't do those problems. Experimentalists and those who do supercomputer calculations take collaboration to another level. The people who study how protons are glued together are hundreds of people working together. You work on your little bit of code and you don't actually have a picture of the whole thing. No one person could write that whole code to do that. They have to be huge teams. In experimental science even more so. "Every paper is written by a thousand people," so physics is very collaborative. In terms of the connections between all of these things, I think there's a tremendous synergy between them. Without experimentation there is nothing, because we're trying to understand reality; otherwise, this would just be math. They are absolutely the backbone of our field.

Q: That brings up the question. Oftentimes, the math of the theories reveals counterintuitive, weird quirks of nature. As a theoretician, do you trust what the math says or do you just fall back and wait for experimental results?

A: You do wait for experimental results, of course. I don't believe anything unless it's consistent with experimentation. But experimentation doesn't make it seem more reasonable. All of quantum physics was built out of experimentation, but experiments are very indirect. If you think about how we learned about quantum phenomena, they were just measuring the spectrum of different gasses. They would just heat them up and then look at the light and pass it through a prism. They weren't really accessing the strange underlying reality; they were just observing stuff and then it was the theoreticians who wrote down equations to predict those spectral lines. And in the process of trying to understand those equations, they arrived at this bizarre interpretation.

Should you believe this bizarre interpretation? In the process, everyone has heard of this bizarre interpretation of Schrodinger's cat, that he might

be dead and alive. Schrodinger didn't believe that, so once he wrote down the equation and realized this was the most natural interpretation of these equations, he said, "I am sorry I had anything to do with it," and he really did exit the field right there. He never wrote another paper on quantum physics again. Einstein didn't believe in it either, and he spent the rest of his life writing very incisive and insightful critiques of quantum physics. So thanks to Einstein and other people, they eventually came up with experiments where you could really test whether these things such as Schrodinger's cat and entanglement could actually be tested. In some sense, it's not really proper to believe in quantum mechanics. It was proper to be skeptical until those tests were done and they have been done now. There is this back and forth between the experiments and the theory. Neither would be complete without the other. Experiments would just be a bunch of speculation without the theory, but the theory is unbelievable until it makes predictions that let you say that this strange stuff is really true.

Q: What's the difference between continuous and discrete in physics? Are those both simplifications or is one correct and the other is wrong?

A: That's a very deep question. We don't know. But the shallower answer is that the world does seem continuous. The space around us seems continuous and time doesn't seem to go around jerkily. You have clocks where the hand jerks around every second and it jerks forward but this isn't our perception of time. Like we were in that moment and then suddenly we're in the next moment and so on.

Many things seem continuous, but then they are not necessarily. Like we know this table, which feels nice and solid and continuous, is really made of individual atoms. And these atoms aren't really like individual billiard balls, but they are these puffy clouds of quantum stuff. The solidity and continuity of things which is apparently there isn't really there.

What we have is a moving target. We don't have a theory of everything and I don't expect we ever will. So it's just what is our best understanding of what the universe is today. And in our best understanding of the universe today, which is called the standard model plus Einstein's Theory of General Relativity. Our best understanding of reality is that space and time are truly continuous, but of course things like solid objects that seem continuous are not. So that is what we know about reality but someday we might find that space is not what it seems. In fact, almost certainly it is not what it seems.

The weird thing is that what we perceive emerges from the much stranger underlying reality. So I expect that some day we will have some new insights into what space and time are, but in the meantime, it is a practical thing that sometimes it is more helpful to use a continuous model. As an engineer or as a 19th century physicist, if you're interested in the flow of fluids, you'd just write down these equations, called the Navier Stokes Equations, that treat fluids as a continuous thing. You're treating everything—space, time, a fluid—as continuous. In the 19th century they actually didn't know for sure if fluid was continuous or not. Now we know that it's actually just an approximation, but it's a good one. Conversely, at other times it's good to discretize things. So even space and time are sometimes convenient to treat as discrete because that makes it easier to put it on a computer.

Q: Do you believe that the discrete approach has gained more prominence in the past couple decades because it is easier to compute?

A: Well, yes and no. Yes, computers have become much more prevalent, and the need to discretize equations has emerged. If you want to solve the fluid mechanics problem, you might want to discretize space and time and then have discrete equations to deal with. But Newton did that. He was trying to analyze waves and didn't actually know how to solve partial differential equations, but he did know how to solve differential equations, so he discretized space and time. He made a huge system of differential equations. He modeled

waves as systems of balls connected with springs. So this idea has occurred to people before.

But of course it was better to invent partial differential equations and subsequent to Newton, people did that. But now on a computer we do find it useful to discretize. There are some interesting, unexpected problems that come up in the process. It turns out when you try to write the quantum mechanics of quarks in a discrete space time, you actually can't. You would think you could write down some discrete version of the continuum theory. And somehow they could emerge from each other, just like you can discretize fluid mechanics and how continuum fluid mechanics is just the continuum limit of the discrete theory. But you can't do that with Quantum field theory. The reason they can't calculate this is that the quantum lattices have an extra copy of every particle. So they have to deal with that and make these extra copies and eliminate them when they try to connect to experiments.

Q: What is the most challenging part of being a researcher? Is it believing what you are saying is true sometimes?

A: No, I think we are quite good at believing things that are counterintuitive. And how are we able to do that? Sometimes you trip up because your instincts and intuition are not in accord with reality. But mostly, math is the crutch. So the reason I have any intuition about the classical world, not the quantum world, is because we live in it. For some reason when you deal with macroscopic systems, the quantum phenomena have all disappeared and we live in the world of everyday common sense—classical physics. I have a good intuition about that, although, even in the classical world, our intuition isn't always perfect and there are non-intuitive things about Newton's Laws or Maxwell's equations.

Maxwell's equations are pretty bizarre. This whole thing about invisible fields that surround us, it sounds like something like the Force from Star Wars, except it's reality! There really are these invisible force fields. I think even common sense classical physics is somewhat counterintuitive.

And the way we cope with that is ultimately we don't rely on our intuition, but we rely on solving a lot of problems like our homework problems. You develop some intuition about what electrical fields will do even though you can't see them. And you develop some intuition about what mechanical systems will do. I guess you could get that out of experience, but you also get that out of solving a lot of physics problems. That's how we build our intuition for the quantum world. If we come up with an outlandish theory that isn't standard, we are accustomed by now to build our intuition not by experience, but by math.

Q: To pivot, you mentioned your fractal analysis of art. You've also done statistical language processing, epidemiology, and work in plenty of other fields that are not the staple domains of physics. What made those problems attractive to you?

A: The Pollock project first demonstrated that it was possible to do this. We wrote a paper that generated quite a bit of interest, and I felt like we made a real contribution to the field. Those paintings may or may not have been authentic, but we were able to show that fractal analysis wasn't relevant. And in that way we were able to further the discussion around those paintings. I think it was the realization that you can contribute outside of physics that was kind of exciting. I was always interested in doing that, so that gave us the permission to keep doing that.

Q: What are your steps when you are researching a problem? How long do you spend reading the textbooks versus working on your model, etc?

A: Especially if you are doing work outside of your field, there is a learning overhead. If you're going to work outside of your field, it's good to talk to the experts in the field, but you also have to become an expert yourself. You can't outsource this work. In interdisciplinary research, you have to spend a lot of time learning stuff, but it's also an easy form of avoidance. It's so easy to read textbooks and do textbook problems. You can avoid the really hard part of just sitting down with a blank piece of paper and confronting something no one knows

the answer to and shaping the question. It's not even a well defined question. It's such a hard thing and learning can sometimes be such a great way to avoid it and still feel like you're working on the project. It's a balancing act. I've got these two really fat books on Solar System dynamics with enticing titles such as Solar System Dynamics that have pictures of Saturn's rings, and people have tried to understand why there are gaps in them, why they have the gaps they do, and why they have these radially pointing spokes as well. So I wish I could just take a holiday and read them cover to cover. But we have to draw the line because we also want to and have to worry about other people jumping in who are experts in this field, maybe teaming up with experts in the other field we are bringing here.

"It's hard to believe that you can do the things that you want. But it turns out you can if you go for it, so I think you should."

Q: Does it always feel like a mad dash when you are doing research to just get it out?

A: It can sometimes feel like a mad dash. When I was in condensed matter physics, I used to work on a lot of these mad dash problems and I've tried to move away from that as I've gotten older. But the maddest dash I've ever done, that in retrospect seems to have been a mistake, was in 2014. It was this long awaited thing that people really dream about. We have this creation myth about how the universe started. In popular parlance it's called the Big Bang Theory, but cosmologists call it the inflationary hypothesis. Some cosmologists have a lot of hubris and don't call it the inflationary hypothesis, but they call it "inflation" like it's an established fact. It's the idea that the universe was expanding in its earliest epoch.

According to the theory of inflation, the universe would expand, and so spacetime would expand uniformly but also through quantum mechanics cause some tremors in space time that are gravitational waves. These primordial gravitational waves were enormous in the early universe,

but they died out. Actually they might still be observable, not by LIGO, but by its descendants. There is one called LISA [Laser Interferometer Space Antenna] which is supposed to go up in a few years. And there is something called the Big Bang Observer. I don't know when it'll ever go up, maybe 2035. Those could directly observe the primordial gravitational waves if it's there. But there's another way that you could observe it—it might get imprinted on the cosmic microwave background, which is the best source of information we have about the early universe.

The cosmic microwave background was created about 400,000 years after the Big Bang. The gravitational waves stream through space, and they imprint themselves on it. So you can look back at the moment of creation so to speak. In 2014, they thought they had observed this signal of primordial gravitational radiation. We didn't sleep for 48 hours, and we wrote a paper about something one could learn from this data. It turned out this was a complete mistake and it was really embarrassing because they had announced it. Not for me personally, because our paper was one of hundreds that people wrote in response to this incredible discovery. It probably would have been one of the greatest discoveries in all of science were it real, but when they are observing the cosmic microwave background, they are looking for a very particular pattern on it. But the same pattern is caused by all sorts of foreground effects that they have to worry about.

In most science you talk about the background noise, but in Cosmology, you talk about the foreground noise because you're trying to look into the past and everything that happened after it is in front of what you are looking at, and that is the foreground. So you have to somehow get rid of the foreground, and it turned out that what they were observing was actually dust in a galaxy. This is exciting for the handful of people who study dust in the galaxy, but for everyone else, it was a great disappointment and a great embarrassment because they had gone very public with this discovery announcement. For such an important matter, they were careless in estimating their foregrounds. They were in such

a rush to announce it. They couldn't wait because there is this European collaboration called Planck which is a satellite that was collecting exactly the kind of data they were needing to estimate these foregrounds, but they were taking their own sweet time and they weren't sharing their data with the BICEP (Background Imaging of Cosmic Extragalactic Polarization) collaboration. BICEP partially fudged the data and someone took a picture of the Planck data at a talk with a phone camera, which you can imagine introduced distortions into the plot. That's where they got it all wrong.

Q: Do you have any advice for young scientists and undergraduates?

A: I guess I should avoid the clichés like, “go for what interests you,” although that is certainly true. I've learned in my own life that you can. And I hadn't realized that that was possible. I think you, surprisingly as a young person, are much more conservative or unsure about what is possible. It's hard to believe that you can do the things that you want. But it turns out you can if you go for it, so I think you should.

The other advice I would give is, and this is specific to Case undergrads, that you have a lot of opportunities on this campus and you should make sure to seize them, but they require effort on your part. It's almost never going to happen that someone comes up to you and asks you, “Hey, do you want to work on a research project with me?” so it's up to you to identify who you might want to work with and then go out and make that happen. And explore widely as an undergraduate because there is going to be a period afterwards where you will have to narrow down. I think that was true in my life and it has to be true in anyone's life. For a while you have to become an expert in something before you can go back to being an expert in nothing and still make a living at it. So now is a great time to explore widely. Seize the opportunities and make sure you take initiative and also that you explore widely while you are young.



How Emotions in Hearing Testimonies Shape Mental Health Policy-Making: An Application of the Social Construction Theory of Emotion to the Legislative Process

Aarthi Uthayakumar - University of Southern California

BIOGRAPHY

Aarthi Uthayakumar is a recent honors' graduate from the University of Southern California. She is a mental health rights' advocate based in Los Angeles, the founder of USC's Student Psychiatric Association, and a longstanding activist for Amnesty International. She currently works as a program manager for the United States Tamil Action Group, a human rights' organization which works with the U.S Government to bring peace and transitional justice to Tamils in Sri Lanka.

ACKNOWLEDGEMENTS

Words could never truly compose my sincere appreciation and gratitude for the important people in my life who have contributed to my success in creating this body of work. Regardless, I will make a humble attempt to acknowledge those who have supported me in my journey. First and foremost, I would like to thank my extremely loving and supportive parents and my younger brother who have all given me a sense of direction, purpose, and hope when I needed it the most. I am forever indebted to their unconditional love, support, and guidance. Finally, I would like to acknowledge the thousands of children and adults struggling with mental illness in America during these turbulent times. This work is dedicated wholeheartedly for you.

Abstract

Mental health laws (MHLs) in America are designed to ensure the community integration of people with mental health disorders, the ethical construction of mental health care treatments, provision of high-quality care, and easy access to care at the community level. As the number of individuals diagnosed with mental health disorders in the United States continues to increase, the need to pass effective and sustainable mental health legislation becomes increasingly urgent. Efforts to pass such legislation rely heavily not only on political assemblies, but also on the emotions expressed within the statements made during the law-making process. This study uses a content analysis approach and the social construction theory of emotion to better understand how different emotional appeals used in state and federal testimonies are perceived and understood. The results of the content analysis primarily indicate that: (1) lawmakers cannot accurately detect and empathize with emotions in panelists' statements, (2) witnesses with mental illness providing testimonies at legislative hearings receive less engagement from lawmakers than their co-panelists, and (3) emotional appeals from family members were used to push psychiatric solutions for mental health while emotional appeals from consumers were used to push for policies that looked past medical solutions (e.g. housing and jobs).

Introduction

“What is at stake is nothing less than the survival and well-being of a generation of innocents.”

- António Guterres, United Nations

Mental health laws (MHLs) have been legislated by state assemblies across the United States for decades, but their efficiency has been continually subject to criticism. Citizens have expressed that MHLs require reform due to the lack of laws governing critical elements of mental health treatment including involuntary hospitalization and restrictions placed on communication with a patient's family (Sederer, 2013). The lack of accessibility, medical training, and efficient court

proceedings have also been cited as areas in need of reform by rights-based advocacy (RBA) groups such as Mental Health America.

Despite these problems in behavioral healthcare, doctors emphasize that current mental health laws have improved because they have become increasingly multidisciplinary in recent decades (Gopalakrishnan, 2016). Modern psychiatry has advanced beyond the traditional focus on scrutinizing the criminal aspects of mental health, including the insanity plea, fitness to stand trial, and testamentary capacity.

Despite this progress, mental health laws are still in need of reform, as shown by the increasing rates of suicide and mental illness diagnoses in the United States. The most recent data on suicide rates provided by the CDC cites that more than 48,000 people committed suicide in 2018, an increase from 42,773 deaths from suicide in 2014 (CDC Data Brief 355, 2018). With these numbers, the United States has one of the highest suicide rates among wealthy nations.

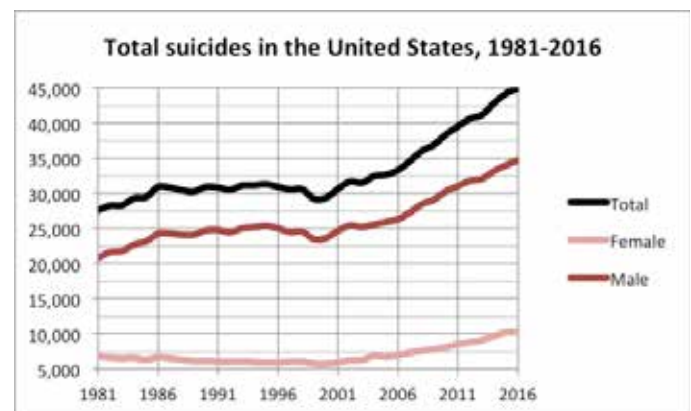


Figure 1. Increase in Total Suicide Rates in the United States (1981-2016) cdc.gov.

Doctors also predict that suicide rates will increase due to the COVID-19 pandemic as a result of psychosocial repercussions of the crisis (Panayi, 2020). The importance of implementing effective MHLs is more pressing than ever. The consequences of the lack of MHLs are at the expense of families grieving loved ones lost to the effects of mental illness. According to a study done on MHLs (including gun laws) in 2015 by the National Institutes of Health, laws have significant

effects in lowering suicide rates that are directly linked to mental illness (Anetis & Anetis, 2015). Thus, while modern psychiatry offers solutions to treat mental illness, the key to reducing American suicide rates could be dependent upon MHLs more so than contemporary medical practices. The notion that MHLs play a larger role than modern psychiatry in addressing suicide rates is affirmed by a 2013 study which finds that inpatient involuntary commitment procedures, the quality and accessibility of mental health services, and the amount of transparency currently [have more impact] and calls for regulation amidst the toxic privatization of the pharmaceutical and behavioral services industries—all of which strongly impact individuals with mental illness and their families (Sederer, 2013).

“While understanding emotional appeals will not eliminate the deficiencies currently present in national and state mental illness policies, it still may be an important tool to improve policy-making in mental health law.”

The Power of Legislative Testimony and its Impact on Law Creation

While many legislative hearings that undergo the rigors of mental-health policymaking are pursued silently, the power of testimony and its ability to affect public discourse and the reformation of laws is still at work. This power is best illustrated through televised congressional hearings. In 1954, army lawyer Joseph Welch openly expressed his frustrations with Senator Joseph McCarthy and his anti-Communist agenda. This hearing resonated with Americans, and the anger prevalent in McCarthy’s testimony encouraged public discourse questioning anti-Communist sentiment and the lives it was affecting. Similarly, in 1966, the televised congressional hearing on the Vietnam War and the placement of soldiers there triggered a public anti-war response. The shocking admission from government officials

that soldiers were being sent to war zones in which they were unlikely to win and the perceived obstinance in their testimonies popularized the national sentiment which vowed to “bring back our soldiers.” These historical moments, followed by the Iran-Contra affair, the Watergate hearings, former President Clinton’s hearings, and the recent impeachment hearings of former president Donald Trump, all elicited strong nationwide emotions, a result of televised emotional appeals from some of America’s most notable figures.

Some prominent female figures utilized emotional appeal in their hearings to persuade national discourse to be sympathetic towards their cause. Their compelling stories of heartbreak, pain, and loss impacted the creation of improved laws and social culture. Understanding how these stories—and their emotional frameworks—operate in the creation of new policies is essential to the betterment of advocacy-related issues being pursued in the modern political climate.

The Importance of Understanding the Emotional Appeals in MHL Creation

Emotional appeals in testimonial narratives and suggestions made at policy-making hearings, while often overlooked, provide a means to analyze state governments and how legislative entities create laws. Understanding how emotional appeals are devised and delivered in the lawmaking process presents an innovative angle as to how RBA groups can better advocate for Americans with mental health conditions. Historical analysis into how emotional appeals have impacted the legal fora of both state and federal legislatures can provide insight as to how emotions have been perceived by lawmakers and how such perceptions may have influenced the creation of current unsustainable MHLs, including involuntary commitment procedures for minors, uninformed consent agreements per admission upon a psychiatric institution, and 5150, which seeks to address all suicidal and homicidal tendencies without listing a specification in public records. While understanding emotional appeals will not eliminate the deficiencies currently present in national and state mental illness policies, it still may be an important tool to improve

policy-making in mental health law. In order to understand the role that emotional appeals may have in state assembly hearings for mental health bills, it is informative to examine past cases in which emotional appeals successfully influenced the party interests presented on the bill. The following section explores the emotional appeals used in political assembly hearings regarding the opioid crisis.

How Understanding the Opioid Epidemic Hearing Can Help to Understand Emotions in the Creation of Mental Health Laws

In 2017, the National Senate Subcommittee convened a hearing to seek solutions for one of America's worst opioid epidemics. In the hearing, a budget proposal endorsed by the White House suggested that the Affordable Care Act (ACA) end Medicaid expansion and convert federal Medicaid funding into block grants to states (The National Council). This proposal would result in tremendous cuts to the Medicaid program. In response to this proposal, former Congressman Patrick J. Kennedy (D-RI), a witness at the hearing, stated the following:

I can assure you, there is definitely one thing we CANNOT do, or history will judge this Congress very harshly. WE CANNOT CUT FUNDING TO MEDICAID. That is not a political statement, it is a practical one.... In 2016, suicides claimed more than 44,000 lives. Combine that with the 64,000 lives lost to drug overdoses in 2016 and the total is over 100,000 American lives lost. And God only knows how many other lives were torn apart or shattered due to the trauma brought upon by these tragedies. Do the math: nearly 300 people die EVERY SINGLE DAY due to brain illnesses. What are we doing for this crisis? Not nearly enough. Talking and reporting about this crisis is not enough! Hiring expensive agencies to create national advertising campaigns is not enough. We need real, substantial, emergent dollars – NOW! (The United States Senate Committee on Appropriations, 2017).

In 2018, the House and Senate passed a budget agreement to lift the budget caps and authorize an additional \$6 billion to address the opioid epidemic over the fiscal years 2018 and 2019 (National Council Board, 2019). Over the next two fiscal years, the \$6 billion was allotted for various efforts to address opioid diversion, addiction, prevention, and treatment. The previous budget proposal to which Mr. Kennedy objected at the hearing ultimately lacked the political support to be passed. While Mr. Kennedy's strong emotional appeals of anger and disappointment in his witness statement cannot be causally linked to the refusal to cut funding to Medicaid, his emotions served as the backbone for senatorial discussion arguing the justification of continuing Medicaid expenditures. Mr. Kennedy's witness statement was frequently referred to throughout the hearing, with its significance stemming from the emotions integrated into his argument. The emotional appeals in Mr. Kennedy's argument translated directly to the qualities of the budget proposal itself. Not granting cuts in Medicaid expenditures for opioid treatment was politically favorable because it countered the anger and disappointment that could have arisen had the cuts been pursued. Mr. Kennedy's interests on behalf of Americans struggling with opioid addiction were honored in the committee's decision because he attached strong emotional fervor consistently throughout his witness statement.

Patrick Kennedy's use of emotional appeals to

"...harmful policies affecting those in America with mental illnesses will not be properly addressed unless the testimonies of those affected are acknowledged at the national level."

encourage federal action, which would protect Americans with a drug addiction, offers valuable insights into how emotional appeals can be used to better convey a victim-based and rights-based approach for policy-making procedures. This is crucial in creating more effective mental health

laws. In the opioid crisis hearings, attaching emotions to a legislative suggestion brought positive change for Americans struggling with drug addiction. Similarly, attaching emotions to legislative suggestions may open up new possibilities for more empathetic government actions and policies addressing the treatment and management of Americans suffering from a mental illness. Whether or not such possibilities are valid can be answered by the following research question: How do the emotions of witnesses in testimonies for state and federal hearings impact the law-making process of modern mental healthcare policies?

Literature Review

This literature review is an attempt to summarize the current knowledge about emotions in political testimony and the impact they may have on law and public policy. The expected contribution of this research is to set existing theories on how emotions apply to judicial testimonies and international criminal tribunals as a precedent to state and federal legislative testimony. While a lack of data affects the academic focus on emotions in the legislative assembly, well-established studies on the interpretation of emotion in video and audio cues and the power of emotions in courts and international tribunal testimonies are extended to address the applicability of such foci to the policy-oriented components of this study.

The Power of Emotions in the Lawmaking Process

As stressed by popular congressional hearings throughout history, the importance of testimony and the emotions which have informed them is central to this study. Gillian Whitlock's review essay "The Power of Testimony" (2007) in the journal *Law & Literature* instructs this study's analytical findings on why emotions matter in policy-making and law. Whitlock's essay examines five case studies on international atrocities analyzed in Schaffer and Smith's book *Human Rights and Narrated Lives*. She frames these studies to reveal the importance of witness testimony on restorative justice and human rights.

While the proposed research examines the power of testimony in the context of American policy-making, Whitlock's analyses nevertheless explain and support the findings of this study. Just as human rights violations are often overlooked until brought to an international platform, harmful policies affecting those in America with mental illnesses will not be properly addressed unless the testimonies of those affected are acknowledged at the national level. In Whitlock's analysis, the emotions in the testimonial narratives of victims of human rights abuses were found to significantly shape human rights discourse on an international scale. For example, the emotional devices used by women who were brutally oppressed by the Taliban regime significantly influenced the world's view of female oppression in the Middle East and impacted further testimonies given by women in similar situations.

Furthermore, Whitlock suggests that the "codings of life narrative" is overlooked in academia but should be subjected to further study because it informs a critical understanding of the "production, circulation, and reception of trauma story" that emerge from the victims of some of the world's most unspeakable atrocities (Whitlock, 2007, p. 146). Whitlock's findings demonstrate the impact that emotions from persons with mental illness testifying before law-making entities may have on legislative bodies. Just as testimonial narratives of pain, loss, and heartbreak can initiate discourse about an area of international conflict, the narrated lives of people in America with mental illnesses could help reform the negative stereotypes informing modern public discourse as well as that discourse's impact on unsustainable healthcare legislation and initiatives.

A critical extension of Whitlock's analysis is supported by Joshua Karton's work on the legal implications of interpreted testimonies at international criminal tribunal proceedings. In his piece, *Lost in Translation*, Karton explains that error in emotional interpretation by courts violates the rights of international criminal defendants and negatively impacts the attestation of a fair trial. Furthermore, he notes how emotional appeals used by categorically different witness groups are

interpreted with variance. Some appeals, such as victim appeals, are valued more and are less prone to being received as inaccurate than, for example, a criminal defendant's appeal. Karton's analysis shows that differences in witness group labels may correlate with differing emotional appeals used in legislative hearings.

This correlation is a key focus of this study and is further supported by the findings of Rosemary Byrne from her work in testimonial evidence in asylum proceedings at international criminal tribunals. Byrne (2007) assesses the issue of credibility bias in testimonies of asylum proceedings. She finds that decision-makers often fail to adapt to the determination process to account for the realities of refugees presenting their testimonies in legal fora, directing proceedings with a 'presumptive skepticism' of claims. Byrne's conception of presupposed skepticism is central to the evaluation of testimony of people with mental illnesses during American legislative proceedings. Testimonies delivered by persons with mental illness are viewed with less validity by decision-makers in national legal fora than testimonies delivered by those without mental illness. This tendency explains why the testimonies given by persons with mental illness do not translate to effective MHLs that address the issues of people suffering from mental illness.

Perception of Testimonies by People With Mental Illness

While the aforementioned literature assesses the impact that emotions can have in judicial and legislative processes, further research is needed to expand our understanding of how persons with mental illness communicate their emotions during testimonies in policy-defining hearings. While there is a deficit in information regarding how psychological disabilities have communicative implications in legal fora, studies that assess political decision-making through other forms of psychological impairment can be applied. For example, Gail Goodman's study on how child testimonies are perceived in criminal court (Troxel et al., 2009) serves as a comparative example in understanding how testimonies by people with mental illness are perceived by

lawmakers. Goodman argues that a child's fears and anxieties are reflected in the emotional nature of their testimonies. In a similar way, when people with severe mental illness testify before legislative bodies, their fears or anxieties may impact their testimonies. Additionally, children's involvement in the legal process proves similar to that of people with mental illness. Goodman's study found that child testimony is often perceived as less credible than that of an older victim due to the assumption of unreliability attached to a child's developing brain. As a result of this perceived unreliability, the testimonies of child victims are easily deconstructed by the argument that said testimonies are infected with false memories. This presumption was recently proven false by a data-driven study conducted by the National Institutes of Health which verified that "the principle that children's testimony is necessarily more infected with false memories than adults' and that, other things being equal, juries should regard adults' testimony as necessarily more faithful to actual events is untenable" (Brainerd & Reyna, 2012). Similar misrepresentations are prevalent in beliefs about testimonies given by people with mental illnesses. This study demonstrates that the testimonies of people with mental illness receive significantly less engagement, credibility, and, consequently, less testimonial weight than those given by their co-panelists. A nationally representative study analyzing the public's perception of people with psychiatric disorders found that those with stigmas found people with mental illnesses to be incompetent, less reliable, and more prone to falsifying information and physical disruption than people who were not diagnosed with a psychiatric disorder (Corrigan & Watson, 2007). However, parallel to Brainerd & Reyna's findings which advocate for the credibility of child testimony at trial, a qualitative study done on witnesses with mental illnesses at judicial proceedings found that people diagnosed with mental illness were equally capable of giving well-informed, competent, and emotionally constructive testimonies as their non-diagnosed peers (Slobogin, 2009). These findings indicate that the stigmas associated with mental disorders create similar presumptive skepticism of testimonial narratives given by those with mental

illnesses as they do of child victim testimonies. The testimonies of both groups are subject to increased skepticism due to an impression of incompetence which unfairly results in lack of regard and testimonial weight by lawmakers and judges. This lack of regard has dangerous consequences in the lawmaking process; without the testimony of people affected by MHLs, potential improvements resulting in more sustainable laws are ignored. A comparison between Goodman's work on child testimony and studies of testimonies by people with mental illness is central to the formulation of a hypothesis which questions whether one's status as psychologically impaired warrants a lack of credibility in their testimonial narratives in contemporary legal fora.

"...witnesses with mental illness testifying before a legislative body are perceived differently and more negatively than co-panelists who are not diagnosed with a psychiatric disorder."

Theories of Emotion

This study requires the application of existing theories of emotion to understand how emotions are socially constructed, perceived, and labelled in testimonies at legislative hearings. Three theories of emotion are integral to understanding this application: the social construction theory of emotion, the psychological theory of emotion, and the neuro-construction theory of emotion. Identified by Dr. Lisa Feldman Barrett in her book *How Emotions are Made*, the social construction theory of emotion "studies the role of social values and interests in determining how we perceive and act in the world" (Barrett, 2017, p. 52). In the context of this study, social construction theory offers an explanation as to how emotions in hearings are triggered differently according to one's role in society. The feelings and perceptions from a testimony by a mother who has lost her child to suicide would differ significantly from a police officer who may be advising law makers

to further criminalize individuals with mental illness for the sake of public safety. However, the social construction theory has its limitations. While social construction theory analyzes how social circumstances contribute to emotional construction, the theory does not consider how those circumstances affect neural circuitry. This is where the equally applicable neuro-construction theory of emotion supplements this study. A comprehensive understanding of the neuro-construction theory is essential in understanding communicative relationships in the legal fora. For example, an emotional testimony from a psychiatric patient may be perceived differently by a senator who has had negative experiences with people with mental illness than one whose son has a psychiatric disorder. These incongruities, according to neuro-construction theory, are the direct result of a biological trigger operant through a molecular mechanism. Different perceptions about mentally ill people are a result of different synapses firing in the brain generated by differing past experiences.

The psychological construction theory of emotion is a combination of both the social and neurological frameworks. This theory advances the idea that conceptual constructions of emotion are based on the immediate situations or environments from which they emerge. The psychological construction theory, the neuro-construction theory, and the social construction theory of emotion combined suggest that emotions are neither universal expressions nor hardwired brain reactions. Rather, they reveal that emotions are merely predictions the brain generates based on one's experiences. These experiences and interactions inform psychological and neurological predictions which ultimately allows one to decide how to react or assess a reaction and consequently express emotion. Barrett applies this idea directly to judicial decision-making, making her findings on emotions relevant to the lawmaking process as well. In her book, Barrett asserts the dangers that come with a classical view of emotion—or essentialism—in American law. She argues that the pursuit of justice in the courtroom is not one that can be carried out in its entirety because some defendants receive undeserving

punishments as a result of their inability to show emotion in a way that is universally acceptable and recognizable. The stone cold face of a serial killer at trial, for example, cannot be accurately analyzed or detected as remorseless by the jury because such detection is baked into the essentialist view of human emotion. Furthermore, what a single juror may see as remorseful is simply the juror's subjective construction of past expressions of remorse, and not an understanding of how the defendant expresses and understands remorse. These inconsistencies in emotional communication have the unjustified power to bring about wrongful sentencing and other obstructions to the pursuit of justice. Although such facets of our legal system should remain focused within the judicial sector, this study examines the possibility of their extension into legislative policy-making. Barrett's findings on emotions in the courtroom directly apply to emotions in state and federal hearings. The way a judge makes an unjustified decision in sentencing a defendant due to a classical view of human emotion parallels how a state legislator may make an uninformed decision to discredit a witness testimony because of the inability witnesses with mental illnesses may have in expressing their emotions in a way.

Interpreting Emotions Based on Video and Audio Cues

While theories of emotions and their contribution to various legal processes are fundamental to the framework of this study, the content analysis design created to answer the research question cannot be fully understood without a comprehensive study of what past literature has said about the interpretation of emotions based on visual and auditory cues. Paul Ekman, a psychologist with expertise in emotional cues, explained in his 2003 work *What is Emotion?* that only some emotions can be accurately detected via facial and vocal recognition. The evaluation of vocal response, according to Ekman, is one of vascular and muscle tonus changes of the vocal apparatus in the context of psychological construction. Similarly, facial responses such as flinching, turning, and forward thrusts are qualities that are often prone to subjective interpretation. With these variables in mind, it is important to note that all of Ekman's

factors are relevant in the creation of emotional labels explicitly marked during the testimonies sampled in this study. Furthermore, in accordance with Ekman's understanding of emotional theory and interpretation, the subjective experience – while commonly deemed irrelevant in modern psychology – is significant both to the interpretation of emotions in general and their contextualization in this study because it “includes sensations that are the result of feedback from changes occurring in the already named response systems” (Ekman, 2003, p. 122). Named response systems, according to Ekman, include, but are not limited to, subsumed memories, images, and expectations associated with emotions. Ekman's interpretation of verbal and facial responses and the emotional cues they both exude apply directly to the content analysis design of this study which samples testimonies from visual and audio sources that are interpreted by the researcher with emotional subjectivity.

How Emotions Matter in Audio and Visual Testimonies by Persons with Autism Spectrum Disorder

While literature on emotional interpretation of witnesses with mental illness in legal testimony is lacking, sufficient study has been completed on emotional appeals used by people diagnosed with autism. An investigative study done in 2014 examined emotions in eyewitness testimonies by people with autism spectrum disorder (ASD) (Maras & Bowler, 2014). The researchers found that certain facial responses, such as facial spasms or excessive blinking, in addition to vocal responses like tonal changes, indicated frustration associated with memory difficulties that are often described as a common symptom of ASD. Similarly, people with severe mental illnesses often experience distinct physical responses which can be interpreted alternatively in an emotional context compared to an essentialist view. For example, people with schizophrenia are commonly misinterpreted as being emotionless, but certain physical indications such as shaking hands or the clenching of the fists can commonly be noted as expressions of nervousness, tension, or frustration (Mandal, 1998). These findings were utilized when interpreting emotional appeals

used by patients expressing their schizophrenic symptoms and the collection and labelling of such appeals.

Hypotheses

To categorize the findings of the main research question, three sub-questions are posed followed by three corresponding hypotheses. First, when mentally ill people testify before a committee are they perceived differently than other panelists who do not have a mental illness at a reformative hearing? Second, do emotional appeals differ amongst the different witness groups? How so? And third, what types of solutions are the emotional appeals being used to push? and how do these solutions differ amongst witnesses who have had mental illness in comparison to witnesses who have not?

The first sub-question is directly substantiated by Karton and Goodman's work on testimonial credibility and Dr. Barrett's work on emotion and the law. The literature upholds the fact that children and criminal defendants are perceived differently due to a presupposed notion of emotional incompetency and unreliability. With this noted, a parallel hypothesis—in the context of mentally ill witnesses—was drawn: witnesses with mental illness testifying before a legislative body are perceived differently and more negatively than co-panelists who are not diagnosed with a psychiatric disorder.

Additionally, the second sub-question directly addresses the findings of Whitlock and Karton as well as the six classifications of witness groups (which are addressed in further detail in the data collection and methods portion of this study). The literature previously discussed on international tribunal criminal proceedings suggests that the emotional appeal of statements given by victims of war crimes are notably variant from international criminal defendants. The second hypothesis which poses parallelism of differences in emotional appeal for human rights' abuses hearings to witnesses with and without mental illnesses in American lawmaking hearings is as follows: People affected by unsustainable MHLs including

family members, founders of nonprofits, and psychiatric consumers would reveal significantly different emotional appeals than that of witnesses who have not been directly affected by such laws. These witnesses include law enforcement, for-profit medical industry workers, and government workers.

The aforementioned hypothesis, if found to be consistent with the findings, could also be sufficiently explained by Barrett's application of construction theories of emotion to law because the reception of an emotional appeal from a lawmaker is subjected to the same inaccuracies and vulnerabilities of detection that the production of an emotional appeal from a witness's end may elicit.

The third sub-question centers not only on the operant mechanisms of emotional appeals but also the implications it has in pushing forward policy agenda. A study by Gerald Grobe, an American mental health policy expert, suggests that individuals with mental health issues often advocate for solutions that center around job and home security as well as financial help in educational and career needs. Psychiatric patients have time and time again experienced the disastrous deficits of quality care in the behavioral health industry. Because the system has wronged these individuals so many times, patients or consumers tend to find efficiency in solutions that are not completely dependent on the reformation of America's broken medical system. On the contrary, Grobe's study revealed that while consumers themselves were not fans of healthcare advocacy, parents and family members who were mental health advocates favored solutions that directly endorsed both the failures and successes that come with privatized behavioral care. These discrepancies in advocacy goals automatically call for differences in emotional appeals which push varying policy agendas. Based on the established frameworks, the following hypothesis is the expected solution to the third subquestion: persons with mental illness will push for solutions through emotional appeals that do not require psychiatric care. Other panelists will push for solutions that involve psychiatric care.

Witness Classification	Examples
Law Enforcement Officials	District Attorneys, Sheriff Deputies
Non-Profit Organizations	Mental Health America, Kennedy Forum
Bureaucratic Entities (Not including law enforcement)	State Department of Behavioral Health and Intellectual Disability Service, Members of the U.S. Department of Health and Human Services
Psychiatric Patients/Consumers	Bipolar, Schizophrenia
Family Member Allies	Parents advocating on behalf of their children, Parents who's children have committed suicide
For Profit-Medical Industry Workers	Private Psychiatrists Health Insurance Company Representatives Pharmaceutical Company Representatives

Figure 2. Witness Classification groups and examples.

In its entirety, all three sub-questions and the hypotheses which offer predictions for them provide a more categorized and organized approach to the main research question central to this study. The implications that the stated hypotheses could have on mental health policymaking and the legislative process which it generates are tested through a thorough content analysis approach.

Data Collection and Research Methods

This section explores the content analysis research which compared and analyzed emotional appeals used in testimonies from multiple state and federal legislative hearings across the United States from 2014 to 2020. A content analysis approach was the best method to study the main research question since this allowed for a more thorough comparative analysis of hearings and their witnesses throughout time and for the effects of emotional appeal to be studied on a broader scale.

Sample Selection

Over twenty different testimonies at legislative hearings were selected and analyzed for this study. The testimonies were selected based on the researcher's interpretation of availability,

medium, witness classification, and significance in impacting modern mental healthcare policy. The media of the hearings sampled were both video and audio records. For the purposes of this study, hearings which were only available via transcript were not analyzed since text cannot convey a subject's emotional appeal as effectively as voice or facial expression (Werwick & Shah, 2014). Furthermore, Ekman's analysis of facial and vocal response detection in human emotion could not have been applied comprehensively. All of the examined testimonies were from mental health policy hearings from the years 2014 to 2020. This time span displays relevant contemporary legislation which has had a significant impact on people with mental illness.

The sampled testimonies are from three different types of hearings: budget hearings, investigative hearings, and policy improvement hearings. The budget hearings were primarily centered on how state and city budgets could be better distributed to serve the needs of citizens with mental illness. Investigative hearings scrutinized state noncompliance with parity laws and the effect noncompliance may have on people with mental illness. Policy improvement hearings primarily focus on what measures government programs can introduce to ensure that the intentions of a

policy are met, how the problem of mental illness in homeless communities is addressed, and how marginalized communities struggling with mental illness can receive access to equal healthcare treatment.

All testimonies sampled were given by witnesses who can be categorized into six distinct classifications as illustrated by Figure 2. The witnesses are either law enforcement officials, employees of non-profit organizations, employees of bureaucratic entities other than law enforcement, consumers or psychiatric patients, family member advocates, and privatized medical industry workers. Witness classifications were not chosen or determined prior to the selection of the hearings. Rather, the classifications are an accurate reflection of the witnesses involved in prominent mental health policy hearings. Furthermore, specific keywords were entered into federal databases to obtain relevant hearings. These keywords included: mental health policy hearings, behavioral health hearings, civil commitment hearings, involuntary hold hearings, state policy mental health redesigning, mental health informational hearings, mental health oversight hearings, mental health coping policies, bills on substance use and recovery, executive budget proposals (mental health), federal mental health legislation, mental health access improvement, mental health housing act, parity law noncompliance hearings, and health care costs hearings. These keywords were input into U.S. Senate archives, the National Archives on Congressional Hearings, and Legislative Archives of the federal government.

Research Methods

The primary research methods used both quantitative and qualitative content analysis. Human coding was used to unitize the content analyzed, and thus the research method was heavily reliant upon the researcher's interpretation of discrete emotions, reactions, and facial expressions. This type of interpretation posed a limit to this research method and will be explained in further detail in the limitations section. Appendix A, shown in Figure 4, codes the following

qualitative variables of the hearings sampled. These variables include: date of testimony, hearing medium, hearing name, the issue or piece of legislation the hearing was set to address, the name of the witness, the witness's classification, the witness's position on the issue at hand, the emotional appeal used by the witness in his or her statement, whether or not the witness openly expressed support for a psychiatric or medical solution, the overall hearing committee's reactions to the witness testimony, and the average time the lawmakers of the committee spent engaging in or discussing the witness testimony. The emotions, which were correlated with the appeal stated on the code sheet, were categorized by a theoretically informed, comprehensive understanding of a combination of the witness's facial expression, body language, tone of voice, and overall mood. Based on the qualitative data, a separate code sheet was formulated to quantify and analyze the relevant information from testimonies. Appendix B and Figure 5 map quantitative variables to each witness classification group. The variables are: number of testimonies given by each witness classification group, and average committee time spent on a testimony per witness group. They also include number of witnesses that support a psychiatric or medical solution per group, % of expressions of sadness and/or worry per witness group, % of expressions of fear and/or concern per witness group, % of expressions of shock and/or disgust per witness group, and % of expressions of shame per witness group. The numeric data produced by this code sheet were then graphed.

Data Analysis and Findings

The analyzed data and the findings which were interpreted from the analysis were both consistent and inconsistent with the aforementioned hypothesis. The first sub-question asked: When people with mental illness testify before a committee, are they perceived differently than other panelists at a reformative hearing? The prediction for this subquestion was affirmative, citing Barrett's work on judicial testimony and Whitlock and Karton's work on differences in perceptions amongst witnesses and defendants at international criminal tribunal proceedings. The

results of content analysis remained consistent with this first prediction. In Figure 6, it is apparent from the sampled testimonies that patients receive significantly less engagement from lawmaking committee members than their co-panelists.

In addition to this finding, content analysis results also indicated that emotional appeals differ amongst various witness groups, as shown in the figures below. While the findings seem to remain consistent with the hypothesis, the emotional appeals – while varying amongst witness classifications – appear to be made in favor of reform and are similar in intent. All classifications, including law enforcement and medical workers, have expressed that they have witnessed suffering due unreformed MHLs. Most of the emotions they expressed in their statements stand in solidarity with that of patients and family members. While entities like law enforcement may not have been directly impacted by unsustainable involuntary hold laws, they have seen the consequences of such laws and testified at hearings to improve them.

Furthermore, emotions like “concern” were labelled and collected based on objective testimonies that used words such as “worry” or “anxious” without much fluctuation in facial or vocal response. The emotional appeal of concern was rather neutral and may have appeared scripted.

The emotional expressions demonstrated by family members were far more nuanced and passionately informed, lacking the scripted feel. As such, they were not labelled to include concern. Most familial testimonies appeared genuine, which brought about more exaggerated and easily identifiable appeals including shame, sadness, disgust, and anger towards the justice system.

Discussion and Conclusion

Limitations of Study

First, this section acknowledges the politics involved in legislative hearings and testimonies. Oral testimonies from witnesses are useful pieces of evidence which committees can collect and analyze to inform legislative policymaking.

The power of oral testimony, which is further explored in the literature review, is also used as a political tool for the agendas of the Democratic and Republican parties. While the testimonies and hearings sampled for this study portray a comprehensive image of witnesses at mental health policy-making hearings, the political agenda behind these witnesses’s appearances – or the subpoenas issued to panelists for investigative hearings – were not taken into account in the overall analysis and interpretation of quantitative results. This lack of record was primarily due to a deficiency in available resources. If an extension of this study were pursued, then the exertion of political influence upon the emotional appeals of legislative testimony could further inform the findings of this study.

In addition to the limitations posed by insufficient addressal of political influence, the issue of researcher subjectivity must also be acknowledged. While the categorization of emotional appeals in this study was theoretically quantified by many emotional tells, such understanding is still vulnerable to human subjectivity. The validity of the overall content analysis is limited because the results were still largely dependent upon the subjectivity of human coding and interpretation. In accordance with Barrett’s theories on emotional perception, researchers’ past personal experiences of emotional expressions like shame, disgust, and anger could affect their categorization of the emotions expressed by the witnesses and lawmakers.

In addition to the limitations posed by insufficient addressal of political influence, the issue of researcher subjectivity must also be acknowledged. While the categorization of emotional appeals in this study was theoretically quantified by many emotional tells, such understanding is still vulnerable to human subjectivity. The validity of the overall content analysis is limited because the results were still largely dependent upon the subjectivity of human coding and interpretation. In accordance with Barrett’s theories on emotional perception, researchers’ past personal experiences of emotional expressions like shame, disgust, and anger could affect their categorization

of the emotions expressed by the witnesses and lawmakers.

Strengths of Study

While there are indeed limitations of this study which must be taken into account when assessing the validity of the findings produced by the content analysis, the strengths apparent in the research methodology must also be acknowledged in the overall assessment. First, this study is replicable and practical since the documentation of all the hearings and the testimonies involved in them are permanent and up to date. Extended research of this study can be done unobtrusively.

Second, the results of the content analysis remain essential to the overall discussion of mental health policy-making. While the validity of the content analysis approach to all political science research is subject to justified questioning due to the nature of the subjective opinion of the researcher, the overall conclusions produced by the research conducted reveal an angle of analysis to policy-making that is crucial for the creation of better and more sustainable mental health laws.

Finally, one of the most notable strengths of this study is the relational analysis of affect extraction. While the evaluation of explicit emotions in a source is subject to the unavoidable element of change over time and populations (Palmquist, 2019), the capturing of the emotional and psychological state through human coding to extract qualitative results speaks to a relational analysis between different witness testimonies which poses a creative design for further experiments that seek to comparatively analyze the relationships between legislative testimony. Furthermore, Ekman's analysis on the benefits of researching emotions through subjective means could provide validity to the findings of this study.

Implications for the Legislative Process

As the literature review of this study indicates, emotions of witnesses in testimonies are an important factor in the progression of policy into action. The findings of this study indicate that emotions are perceived differently from statements given by people with mental illness

as opposed to their co-panelists without mental illness in reformatory MHL hearings. This inequality in testimony weight has negative implications in the law-making process because suffering caused by ineffective laws is not fully understood. Contemporary legal fora do not sufficiently heed the experience of those suffering from mental illness. People with mental illness have firsthand experience of the consequences of poorly informed and implemented MHLs. Instead of encouraging a witness to talk on behalf of a person with mental illness, state senators and assembly members have a responsibility to acknowledge that they cannot accurately detect emotions in people who have difficulties emotionally communicating crucial information. Acknowledging such a notion has the potential to encourage lawmakers to legitimize the concerns testified by consumers and psychiatric patients and allow such testimonies to directly impact policy.

Further, the findings of this study attest that policy recommendations made by family members advocating on behalf of their loved ones differ from the policy recommendations made by people with mental illness themselves. Policy recommendations that are made by family members or people who have lost someone to suicide, for example, may directly promote or encourage psychiatric and/or medical solutions to mental illness which are lacking proper regulation and have severe, damaging effects on the treatment of mental illness. While this study acknowledges that medical solutions cannot be eliminated or deconstructed, a greater emphasis in the lawmaking process on integrating people with mental illnesses back into society post-hospitalization should be made in accordance with better regulation of behavioral hospitalization.

Finally, the implications of this study can be applied to potential policy proposals which can ensure that people with mental illness have the resources they need to communicate their concerns at legislative hearings. People with mental illness, especially those who are unable to emotionally communicate in adherence with the classist view of emotion in American legal fora, should be provided a therapist

or an expert in emotional communication prior to giving testimony so that they can communicate their positions in a way which lawmakers can easily detect. While lawmakers have a responsibility to understand the hardships that come with emotional communication and mental illness, understanding and implementing this responsibility is likely to progress slowly. Thus, for the time being, individuals with mental illness should be given the resources they need to make sure their testimony has their intended impact. As detailed earlier, the power of testimony is one that should not be taken lightly, and people with mental illness must be equipped with that power when they deliver their testimonies.

Avenues for Extended Research

As noted briefly in various sections of this paper, there are multiple avenues for further research to be conducted using the analyses developed in this study. Extensions of this project can perhaps reduce the potential limitations of the findings. For example, future research can focus on important variables that were not accounted for in the comprehensive analysis of the testimonies including political agenda setting, economic gain, destruction of character, and dynamic shifts in lobbying power. The same quantitative content analysis research design demonstrated in Appendix A could be applied to evaluate the impact of any of these variables on legislative testimony. Furthermore, advancements like applications which use facial recognition technology to detect emotion could be applied in visual testimonies for a more accurate and less subjective interpretation of emotion if such an interpretation is required.

References

- (2010). Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality. <https://www.ahrq.gov/data/hcup/index.html>
- Anestis, M. D., & Anestis, J. C. (2015). Suicide Rates and State Laws Regulating Access and Exposure to Handguns. *American journal of public health, 105*(10), 2049–2058. <https://doi.org/10.2105/AJPH.2015.302753>
- Ayano, G. (2018). Significance of mental health legislation for successful primary care for mental health and community mental health services: A review. *African Journal of Primary Health Care & Family Medicine, 10*(1), e1–e4. <https://doi.org/10.4102/phcfm.v10i1.1429>
- Barrett, L. F. (2017). *How emotions are made: The secret life of the brain*. Houghton Mifflin Harcourt.
- Bergman, D. M. (2013). The role of government and lobbying in the creation of a health profession: The legal foundations of counseling. *Journal of Counseling & Development, 91*(1), 61–67. <https://doi.org/10.1002/j.1556-6676.2013.00072.x>
- Bezanson, R. P. (1975). Involuntary treatment of the mentally ill in Iowa: The 1975 Legislation. 261. <http://hdl.handle.net/10822/772121>
- Brainerd, C. J., & Reyna, V. F. (2012). Reliability of Children's Testimony in the Era of Developmental Reversals. *Developmental review: DR, 32*(3), 224–267.
- Byrne, R. Assessing Testimonial Evidence in Asylum Proceedings: Guiding Standards from the International Criminal Tribunals (2007). *International Journal of Refugee Law, 19*(4), 609–638.
- Darrin (2017). *Content Analysis In Qualitative Research*. Educational Research Techniques
- Corrigan, P. W., & Watson, A. C. (2007). The stigma of psychiatric disorders and the gender, ethnicity, and education of the perceiver. *Community mental health journal, 43*(5), 439–458. <https://doi.org/10.1007/s10597-007-9084-9>
- Cutcliffe, J. R., & Hannigan, B. (2001). Mass media, 'monsters' and mental health clients: the need for increased lobbying. *Journal of psychiatric and mental health nursing, 8*(4), 315–321. <https://doi.org/10.1046/j.1365-2850.2001.00394.x>
- Data Brief 355. Mortality in the United States, 2018 (2020). Federally Qualified Health Centers Prepare for Challenging Path Ahead, CDC.
- Ekman, P. (1971). Universals and cultural differences in facial expressions of emotion. *Nebraska Symposium on Motivation, 19*, 207–283.
- Fassin, D. (2008). The Humanitarian Politics of Testimony: Subjectification through Trauma in the Israeli: Palestinian Conflict. *Cultural Anthropology, 23*(3), 531–558. Retrieved March 27, 2021, from <http://www.jstor.org/stable/20484515>
- Gilmore, L. (2001). *The Limits of Autobiography: Trauma and Testimony*. ITHACA; LONDON: Cornell University Press. Retrieved March 27, 2021, from <http://www.jstor.org/stable/10.7591/j.ctv3s8p46>
- Gopalakrishnan G. Mental Health and Law-Contemporary issues. *Indian J Psychiatry, 2016;58*(Suppl 2):S166-S167. doi:10.4103/0019-5545.196802
- Goodman, Gail S. (2005). Child victim testimonies in criminal court.
- Grob G. N. (2005). Public policy and mental illnesses: Jimmy Carter's Presidential Commission on Mental Health. *The Milbank quarterly, 83*(3), 425–456. <https://doi.org/10.1111/j.1468-0009.2005.00408.x>

Hagen, M. A. (1997). Whores of the court: The fraud of psychiatric testimony and the rape of American justice. The Guilford Press. 38-49.

Jackson, C. (2012). Speech, gender and power: Beyond testimony. *Development and Change*, 43(5), 999-1023. DOI: 10.1111/j.1467-7660.2012.01791.x

NY State Senate (2019). Joint Legislative Public Hearing on 2019-2020 Executive Budget Proposal: Topic Mental Hygiene

Karton, Joshua (2018) International criminal tribunals and the legal implications of interpreted testimony. *Journal of Refugee Law*

Kilbourne, A. M., Beck, K., Spaeth-Rublee, B., Ramanuj, P., O'Brien, R. W., Tomoyasu, N., & Pincus, H. A. (2018). Measuring and improving the quality of mental health care: a global perspective. *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 17(1), 30-38. <https://doi.org/10.1002/wps.20482>

Laub, D. (1991). Truth and Testimony: The Process and the Struggle. *American Imago*, 48(1), 75-91. Retrieved March 27, 2021, from <http://www.jstor.org/stable/26304032>.

Mandal, M. K., Pandey, R., & Prasad, A. B. (1998). Facial expressions of emotions and schizophrenia: a review. *Schizophrenia bulletin*, 24(3), 399-412. <https://doi.org/10.1093/oxfordjournals.schbul.a033335>

Commonwealth Fund (2020). New International Report on Health Care: U.S. Suicide Rate Highest Among Wealthy Nations

Park-Fuller, L. M. (2000). Performing absence: The staged personal narrative as testimony. *Text and performance quarterly*, 20(1), 20-42.

Panayi, Adriana (2020) . "COVID-19 Is Likely to Lead to an Increase in Suicides." *Scientific American Blog Network*, *Scientific American*, 3.

Perlin, M. L. (1985). The Supreme Court, the Mentally Disabled Criminal Defendant, Psychiatric Testimony in Death Penalty Cases, and the Power of Symbolism: Dulling the Ake in Barefoot's Achilles Heel. *NYL Sch. Hum. Rts. Ann.*, 3, 91.

Rosemary Byrne (2007) , Assessing Testimonial Evidence in Asylum Proceedings: Guiding Standards from the International Criminal Tribunals, *International Journal of Refugee Law*, Volume. 609-638

Sederer L. I. (2013). The tragedy of mental health law. *Missouri medicine*, 110(2), 104-105. Slate, R. N. (2003). From the jailhouse to Capitol Hill: Impacting mental health court legislation and defining what constitutes a mental health court. *Crime & Delinquency*, 49(1), 6-29.

Sundararaman, R., & Redhead, C. S. (2008). The Mental Health Parity Act: A Legislative History. *Congressional Research Service*, Library of Congress.

Swigger, A., & Heinmiller, B. T. (2014). Advocacy Coalitions and Mental Health Policy: The Adoption of Community Treatment Orders in Ontario. *Politics & Policy*, 42(2), 246-270.

The United States Senate Committee on Appropriations (2017). Addressing the Opioid Crisis in America: Prevention, Treatment & Recovery

Troxel, N. R., Ogle, C. M., Cordon, I. M., Lawler, M. J., & Goodman, G. S. (2009). Child witnesses in criminal court: Psychological science and the law (p. 150-166).

Warren, C.A.B. (1977). Involuntary commitment for mental disorder: The application of California's Lanterman-Petris-Short Act. *Law & Society Review*, 11(4), 629-649. [doi:10.2307/3053175](https://doi.org/10.2307/3053175)

Whitlock, G. (2007). The Power of Testimony. *Law & Literature*, 19(1), 139-152. Black Congressional Caucus, (2017). Youth Mental Health and Suicide Risk. C-SPAN



Ligand Directed Signalling in Therapeutics

Julia Shield - Queensland University of Technology

BIOGRAPHY

Julia Shield is a third-year student studying Biomedical Science at the Queensland University of Technology in Australia. She is involved in the investigation of physiological concepts and their involvement in disease as well as the applications of biochemical and genetic interventions in the medical field.

ACKNOWLEDGEMENTS

I would like to thank Dr Mark Plenderleith of QUT for his support with this publication.

Abstract

Research investigating ligand directed signalling or biased agonism has uncovered new opportunities for therapeutics targeting multiple diseases. Unlike balanced agonists which stimulate multiple pathways, a biased agonist binds to specific active-state receptors to stimulate a single cellular pathway. The ligand stabilizes receptor conformation with selective binding determined by the unique chemical structure of both receptor and agonist. G protein coupled receptors (GPCRs) enable a diverse range of ligand interactions through recruitment of various intracellular proteins. Activation of either G-protein or β -arrestin mediated pathways influence signalling bias following specific ligand binding.

“The future of biased agonism research is promising as investigations continue for many diseases using advanced biotechnology.”

Biased agonism has widespread therapeutic potential as certain signalling pathways can be stimulated for a desired biological effect while avoiding unwanted side effects. Several biased ligands are under investigation with therapeutic areas across cardiovascular, renal, and respiratory conditions. β -adrenoceptors are key targets for biased agonism based treatments. Deleterious cellular outcomes are avoided by inhibiting G-protein signalling. A number of challenges

limit the validity of current research, such as unexpected propagation bias, production of false positive results in quantitative analysis, and

“Factors essential to the process of biased agonism include a receptor-active state and its interaction with cytosolic-signaling-peptides.”

differing results between animal and human trials. However, the future of biased agonism research is promising as investigations continue for many diseases using advanced biotechnology.

Basic Signaling Mechanisms

Since its discovery in 1998, biased agonism has described the action of a ligand specifically activating one of multiple downstream signalling pathways in a cell. This differs from balanced agonists which bind to the same receptors and activate multiple signalling pathways as illustrated in Figure 1 (Michel et al., 2018; Conibear, 2019). Biased agonists stabilize receptor conformation to selectively stimulate a single pathway, allowing targeted adjustment of cellular function. Biased selectivity is determined by specific structures of the binding ligand as they interact with residues in the receptor, producing conformational change to yield unique functional outputs (Franco et al., 2018).

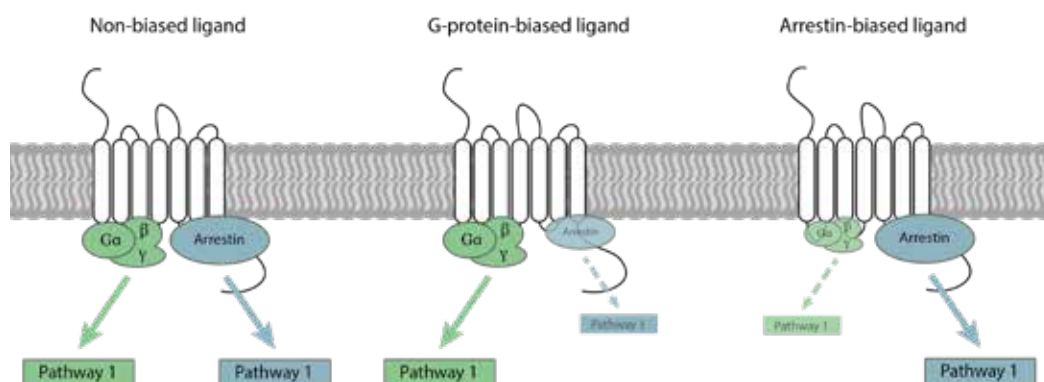


Figure 1. Activation of downstream pathways via balanced and biased agonists. Balanced agonists stimulate multiple pathways following receptor binding whereas G-protein or Arrestin-biased ligands only activate a single pathway (Adapted from Conibear, 2019).

Factors essential to the process of biased agonism include a receptor-active state and its interaction with cytosolic signalling peptides. Stimulation of specific pathways in the cell requires agonist specific receptor conformations. Numerous studies have validated this theory by demonstrating the stabilization of distinct receptor conformations after binding of a ligand (Palanche et al., 2001; Swaminath et al., 2004). As individual receptor regions modify conformation independently, coupling of signalling proteins to the unique receptor segments will produce differential activation of signalling pathways in the cell. Variability in signalling pathway stimulation via the formation of specific receptor conformations is extensively described in current scientific literature. Seven transmembrane receptors express pleiotropic effects with the signalling proteins they are coupled to. With the formation of multiple receptor conformations, ligands stabilise these conformations to selectively enable activated signalling pathways (Kenakin, 2009). This is supported by a study done by Michel et al. (2018) that describes the role of ligand binding stabilising a specific receptor conformation through the use of nuclear magnetic resonance (NMR). Therefore, ligand signalling bias results from the stabilization of specific receptor conformations which independently activate particular signalling pathways and molecules such as G-proteins and β -arrestins (Gundry et al., 2017).

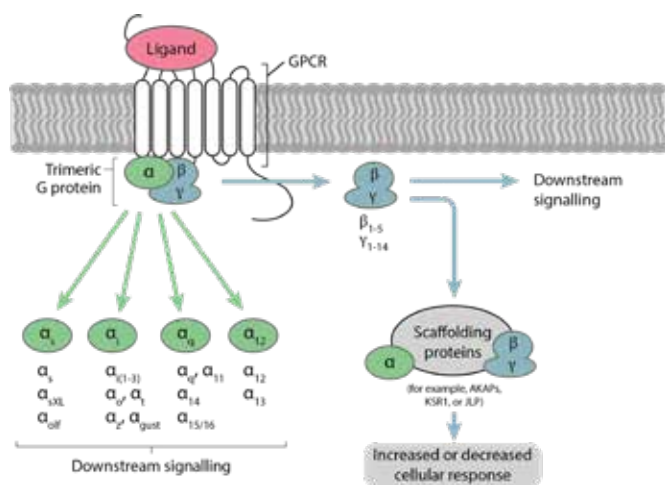


Figure 2. GPCR signalling via downstream proteins for diversification of signalling responses. $G\alpha$, $G\beta$, and $G\gamma$ proteins activate downstream signalling after receptor-binding. $G\alpha$ proteins produce various signals across four families. $G\beta\gamma$ and $G\alpha$ bind to scaffolding proteins which modulates their signalling (Adapted from Wootten et al., 2018).

G-Protein Coupled Receptors

Biased agonism involves GPCRs. These receptors implement various mechanisms which can modify ligand-receptor interaction and subsequent function. Diverse GPCR interactions with various intracellular proteins enable a response to multiple ligands. As illustrated in Figure 2, GPCR-ligand binding activates G-protein subunits $G\alpha$, $G\beta$, and $G\gamma$ which initiate different downstream signalling molecules for diversified responses (Wootten et al., 2018).

Signalling bias is observed following activation of effector proteins G-proteins or β -arrestins after specific ligand-receptor binding. This is because G-proteins activate second messengers, whereas β -arrestins activate MAP kinases. Agonists differentially activate these proteins with opposing susceptibility to internalization, phosphorylation, and desensitisation (Michel et al., 2018). β -arrestins facilitate receptor-trafficking and function as scaffolding molecules to help initiate signalling cascades. Altered receptor conformations following ligand binding induced conformational changes in scaffolding proteins to promote activation of downstream signalling pathways. Ligand-receptor binding produces conformational change in G-proteins which alters the guanosine triphosphate-guanosine diphosphate (GTP-GDP) exchange rate. Ligands inducing a fast rate of GTP association produce more downstream signalling per unit of time compared to ligands with a slow rate as seen in Figure 3 (Wootten et al., 2018). Chemical differences amongst ligands activate distinct signalling pathways due to distinct amino acids compositions within the receptor that couple to stimulatory G proteins (Michel et al., 2007).

As biased signalling can be altered by the location of ligand-receptor binding, the occurrence of

“Signalling bias is observed following activation of effector proteins G-proteins or β -arrestins after specific ligand-receptor binding.”

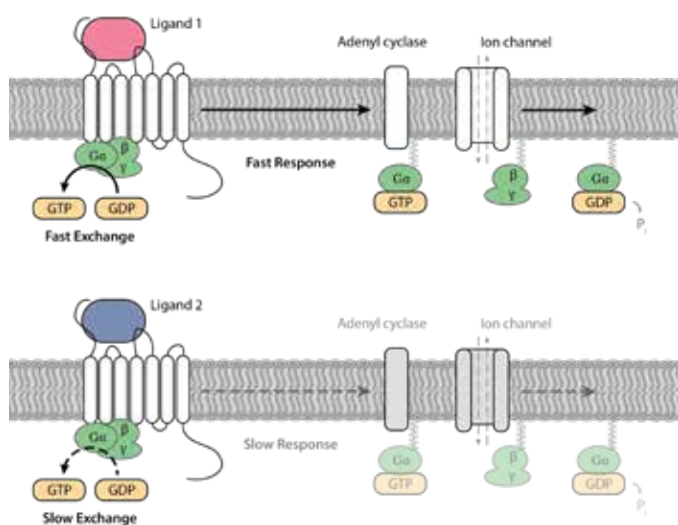


Figure 3. Ligands inducing different conformations within G proteins to produce different GTP–GDP exchange rates. Ligands inducing a faster exchange rate produces more G-protein and therefore downstream signalling events (Adapted from Wootten et al., 2018).

allosteric binding can produce a conformational change for the receptor and lead to biased agonism. Allosteric ligands can work as biased ligands to initiate specific receptor-mediated signalling. Furthermore, an allosteric ligand can activate specific downstream signalling by interacting with the orthosteric site ligand (Hodavance et al., 2016).

Therapeutic Use

Biased agonism has extensive therapeutic potential with drug development by stimulating specific signalling cascades for desirable biological effects while avoiding harmful outcomes as illustrated in Figure 4 (Franco et al., 2018).

For the development of therapeutic drugs with biased agonists, the physiological effects across multiple receptors must be thoroughly determined. Each pathway becomes unique depending on the disease state and bodily systems involved. The seven-transmembrane receptor (7TMR) and GPCR families are key targets for drug therapy. Numerous biased ligands specifically enable β -arrestins and G-proteins via 7TMRs as seen in Table 1 (Whalen et al., 2010; Bologna et al., 2017).

Opioid treatments

Opioid agonists producing analgesic effects are a well-known example of biased agonism in therapeutics. Early research established analgesic effects of β -arrestin2 following opioid receptor stimulation in mice. It indicates μ opioid receptor agonists are biased for G protein activation, becoming beneficial in pain management (Whalen et al., 2010). Findings enabled the development of Oliceridine, an opioid which activates G-protein signalling pathways with an efficacy comparable to morphine. The drug also averts respiratory depression and constipation by avoiding the β -arrestin pathway. A clinical study in 2016 confirming Oliceridine as a success demonstrates the therapeutic potential of biased agonism (Bologna et al., 2017).

Most opioids in clinical use selectively target the μ opioid receptor (μ OR). Patients with chronic pain disorders commonly face undesirable side effects such as constipation, respiratory depression, and drug resistance and dependence. Side effects of μ OR-based drugs were linked to β -arrestin2 pathway signalling as preclinical trials in mice demonstrated β -arrestin2 knockout produced a reduction in respiratory depression and morphine-tolerance (Mores et al., 2019). These findings have influenced the production of G protein-biased μ OR agonists that minimize β -arrestin2 signalling. Therefore, opioids that selectively activate the G-protein pathway such as TRV130 have an improved therapeutic potential for moderate to severe pain.

Ligand	Receptor	Effector Bias	Therapeutic Area
Alprenolol, carvedilol	β 1-adrenergic	β -Arrestin	Cardiovascular
MM07	Apelin	G-protein	Cardiovascular
SII, TRV120027	Angiotensin I	β -Arrestin	Release of inflammatory mediators
Fenoterol, carvedilol	β 2-adrenergic	G-protein & β -Arrestin	Cardiovascular & renal

Figure 4: Biased agonist initiating a desired therapeutic effect on a receptor while avoiding unwanted side effects, compared to a typical agonist (Franco et al., 2018).

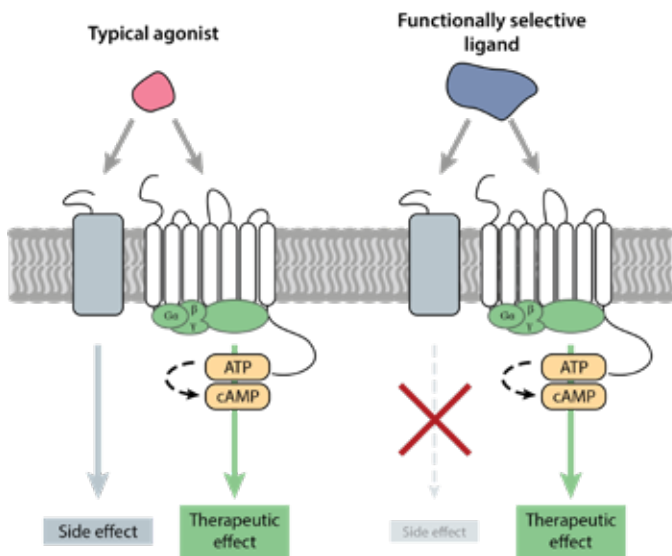


Figure 4: Biased agonist initiating a desired therapeutic effect on a receptor while avoiding unwanted side effects, compared to a typical agonist (Adapted from Franco et al., 2018).

The influence of β -arrestins on opioid analgesia has been the subject of many studies. Mice with β -Arrestin2 knockout experienced prolonged morphine-induced analgesia and an increased hypothermic response compared to wildtype mice. In addition to morphine, heroin produces enhanced analgesic efficacy in the β -arrestin2 knockout mice whereas other μ -OR agonists did not. Together, these studies show that the analgesic efficacy of μ -OR agonists are differentially regulated by β -arrestin2 *in vivo* (Mores et al., 2019). β -arrestin2 knockout mice were resistant to chronic morphine-induced tolerance, which correlates with preserved G protein signalling. This suggests that a G protein-biased ligand provides prolonged morphine-induced analgesia and a reduced tolerance to morphine, resulting in better patient treatment.

β -adrenoceptor treatments

Therapeutic action of carvedilol through biased signalling mechanisms has been closely observed. Carvedilol is a β -adrenergic receptor antagonist used in the treatment of heart failure, myocardial infarction, and angina pectoris. Its cardioprotective mechanism works to decrease vascular resistance by inducing a vasodilation response, involving the relaxation of smooth muscle in blood vessels, causing an increase in diameter (Carr et al., 2016). The drug acts as a biased ligand on β_1 and

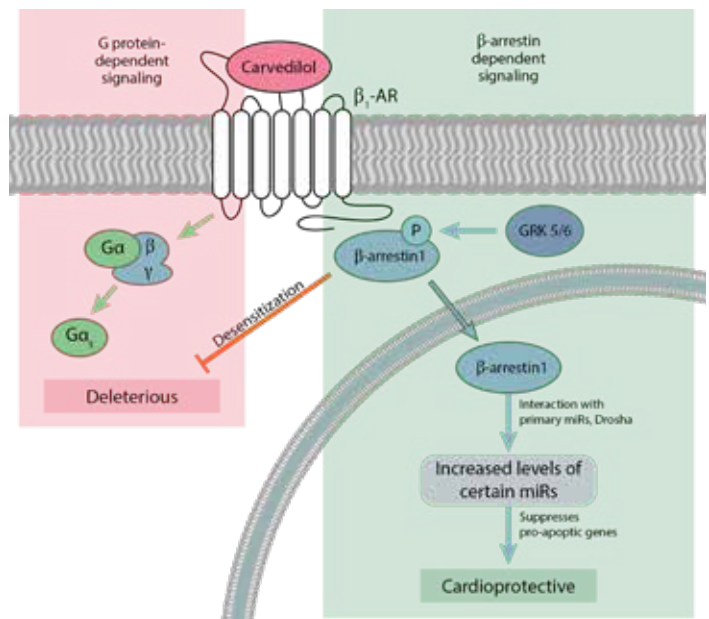


Figure 5: Carvedilol-initiated β_1 -adrenoceptor signalling. Biased activation of β -arrestin in cardiomyocytes stimulates miR subsets and represses pro-apoptotic genes to produce cardioprotective measures. G-protein activation is not induced (Adapted from Bologna et al., 2017).

“Despite findings indicating therapeutic potential, several studies have identified challenges to biased agonism.”

β_2 -adrenoreceptors to specifically stimulate β -arrestin dependent signalling as depicted in Figure 5 (Bologna-et-al., 2017). After binding to β_1 -adrenoreceptors, GRK5/6 phosphorylation of the receptor allows β -arrestin1 to activate five-miR compounds and the Drosha microprocessor complex in the nucleus. GRK5/6 is a G protein-coupled receptor kinase. This leads to initiation of RNA-helicase-miR processing which suppresses pro-apoptotic genes in cardiomyocytes to control myocyte contractility (Bologna et al., 2017). Pro-apoptotic genes encode proteins which have an essential role in the cell death pathway. This process occurs without the activation of G-protein signalling, avoiding deleterious outcomes in the cell.

In the pulmonary system β_2 -adrenoreceptors help regulate movement of the smooth muscle cells in the airways. Therefore, β -agonists are often taken

to alleviate respiratory diseases such as chronic obstructive pulmonary disease and asthma as they induce a bronchodilation response, involving the relaxation of the smooth muscle of the bronchi, thus increasing the diameter and reducing airway resistance. Tachyphylaxis, which occurs when prolonged drug exposure reduces effectiveness, is a major issue in asthma treatment via β -arrestin mediated desensitization (Ippolito & Benovic, 2021). The efficacy of common asthma treatments such as Salbutamol are reduced, producing a decrease in the magnitude of bronchodilation. A reduced response causes asthma patients to become more reliant on β -agonists which increases the risk of damage associated with elevated sympathetic nervous system activity. Tachyphylaxis from β_2 -adrenoceptor activation occurs due to increased downregulation and desensitization of receptors following agonist binding (Matera et al., 2018). This is facilitated by β -arrestins, preventing interaction between the receptor and G-proteins. Phosphodiesterases reduce cAMP produced by G-proteins and block communication between G-protein and receptor, allowing β -arrestin to control desensitization in the cell (Ippolito & Benovic, 2021). Research findings show that β -arrestin2 removal in experimental mice produces a reduction in inflammation when treated with β -agonists relative to an unmodified subject. A reduced inflammatory phenotype could eliminate other factors that contribute to the poor outcomes of asthma patients, such as airway remodelling. It is therefore hypothesized that a biased ligand activating G-protein signalling pathway that avoids β -arrestin activation would not produce tachyphylaxis and act with a higher efficacy (Matera et al., 2018). This has become a growing area of interest in therapeutic research as G-protein mediated pathways in asthma treatment are explored.

Neurological disorder treatments

Biased agonism in drug development has significance in the treatment of nervous system disorders. Specifically, the receptors D_2 Dopamine and μ -opioid (μ OR) are major targets in therapeutic design. D_2 Dopamine receptors were originally used to manage patients with schizophrenia by inhibiting adenylyl cyclase via $G_{\alpha i}/G_{\alpha o}$ which is

a G protein alpha subunit.. Current research has found that β -arrestin2 can regulate the AKT-GSK3 pathway via D_2 dopamine receptors (Gundry et al., 2017). This causes dephosphorylation of AKT, protein kinase B, and alleviates behavioral effects. Lithium drugs are commonly used to target this complex in the management of mental health conditions. β -arrestin2 knockout in mice during experimental trials resulted in behavioral defects as the effects of lithium treatment were lost. A developed β -arrestin biased D_2 dopamine receptor agonist has a greater effect than balanced agonists in the treatment of schizophrenia in mice which suggests the necessity of biased agonists when managing such conditions.

As previously discussed, the μ OR is a target for exogenous opioid analgesic agonists like morphine to reduce pain sensation. Morphine is biased for the G protein-mediated signalling pathway. β -arrestin2 removal in mice has resulted in amplified morphine-induced analgesia compared to unmodified mice. It was found that β -arrestin2 removal in mice protects them from unwanted side effects of analgesic medications including constipation and respiratory depression (Gundry et al., 2017). G protein-biased μ OR agonists have been created to provide analgesia in animal models without such side effects which is promising for future human clinical trials (Gundry et al., 2017).

Cancer cell treatments

β -arrestins participate in multiple cancer-related signalling pathways via several receptor types. The protein β -arrestin1 has a known role in nicotine-induced replication of lung cancer cells using a process with a β -arrestin1-scaffolded complex and nicotinic acetylcholine receptor. Similarly, in cancerous ovarian cells β -arrestins mediate endothelin type A receptor-transactivation which is involved in metastasis activation (Michel & Charlton, 2018). Overexpression of β -arrestin1 in mice promotes tumour angiogenesis and development. As well as initiating proliferative signal pathways in cancer, β -arrestins are also involved in tumour suppression pathways. Transforming growth factor- β inhibits epithelial cell migration via β -arrestin2-mediated activation of the cell division cycle. β -Arrestin2 knockout in mice leads to increased tumour growth

and metastasis mediated by inflammation and angiogenesis compared to wildtype mice (Song et al., 2018). This research demonstrates that the β -arrestins are involved in a variety of cancer related signalling through biased agonism and can provide insight into potential future targets for chemotherapies.

Future Directions

Despite findings indicating therapeutic potential, several studies have identified challenges to biased agonism. These limitations complicate the identification of biased agonists and include an unexpected propagation of bias in data analysis and the need to clarify complicated physiological signalling pathways (Gundry et al., 2017). Techniques for quantitative analysis of bias and suitable screening assays can produce false positive results which skew the validity of obtained results (Michel et al., 2018). The belief that signalling bias is constant across other species implies a potential risk when investigating treatment options, such that animal models may prove problematic for biased agonist discovery. For example, histamine H4 receptor antagonist JNJ777120 has a recognised role in reduction of inflammatory processes via the recruitment of β -arrestin in humans. This conflicted with trials on mice and dogs where JNJ777120 acted as a partial agonist in the $G_{\alpha i}$ -protein pathway, producing a completely different response (Michel et al., 2018). Different functions of the ligand across species has led to increased concern for drug toxicity studies conducted with mice and other animals rather than human samples.

Experimentation with biased agonism continues to evolve. Using a range of technologies, differential activation of G-protein and β -arrestin signalling molecules across multiple receptors continue to be discovered. Most ligands developed are synthetic but these can also be sourced from natural systems. Unique biased agonist profiles continue to be researched to test the effects of agonists and antagonists for many diseases (Kenakin, 2009).

Conclusion

The understanding of biased agonism mechanisms has caused the potential for therapeutic development across a number of diseases to be increasingly promising. Biased agonists are capable of binding specific active-state receptors in order to initiate cellular signalling of a single pathway, inducing a precise response. Activating intracellular proteins such as G-proteins or β -arrestins helps to influence cell signalling bias. As mechanisms involving specific pathway activation become better understood, its therapeutic potential is recognized as a subject for continued investigation. Biased agonism has introduced the ability to produce desired biological effects whilst avoiding undesirable outcomes.

As previously discussed, biased agonism is currently used in many common treatments. The drug carvedilol acts to decrease vascular resistance and help manage heart failure by binding to β_1 and β_2 -adrenoreceptors to specifically stimulate β -arrestin dependent signalling. Similarly, in the respiratory system, treatments such as Salbutamol bind to β_2 -adrenoreceptors to produce a bronchodilation response to manage asthma. Biased agonism has additionally been applied to treatments for neurological disorders and several types of cancer.

However, challenges including false positive results, tachyphylaxis, and lack of clinical trials threaten the validity of current research. As scientific investigation continues into the signalling pathways of β -arrestins and G-proteins via GPCR activation, our understanding will continue to advance with biased agonism becoming an area of interest in the biotechnology field.

References

- Bologna, Z., Teoh, J., Bayoumi, A., Tang, Y., & Kim, I. (2017). Biased G-protein-coupled receptor signaling: New player in modulating physiology and pathology. *Biomolecules & Therapeutics*, 25(1), 12-25. <https://doi.org/10.4062/biomolther.2016.165>
- Carr, R., Schilling, J., Song, J., Carter, R., Du, Y., Yoo, S., & Benovic, J. (2016). β -arrestin-biased signaling through the β_2 -

adrenergic receptor promotes cardiomyocyte contraction. *Proceedings of the National Academy of Sciences of the United States of America*, 13(28), 4107-4116. <https://doi.org/10.1073/pnas.1606267113>

Conibear, A., & Kelly, E. (2019). A biased view of μ -opioid receptors. *Molecular Pharmacology*, 96(5), 542-549. <https://doi.org/10.1124/mol.119.115956>

Franco, R., Aguinaga, D., Jimenez, J., Lillo, J., Martinez, E., & Navarro, G. (2018). Biased receptor functionality versus biased agonism in G-protein-coupled receptors. *Biomolecular Concepts*, 9(11), 16044-54. <https://doi.org/10.1515/bmc-2018-0013>

Gundry, J., Glenn, R., Alagesan, P., & Rajagopal, S. (2017). A practical guide to approaching biased agonism at G-protein coupled receptors. *Frontiers in Neuroscience*, 11(17), 1-6. <https://doi.org/10.3389/fnins.2017.00017>

Hodavance, S., Gareri, C., Torok, R., & Rockman, H. (2016). G-protein-coupled receptor biased agonism. *Journal of Cardiovascular Pharmacology*, 67(3), 193-202. <https://doi.org/10.1097/FJC.0000000000000356>

Ippolito, M., & Benovic, J. (2021). Biased agonism at β -adrenergic receptors. *Cellular Signalling*, 80(2), 109-118. <https://doi.org/10.1016/j.cellsig.2020.109905>

Kenakin, T. (2009). Biased agonism. *F1000 Biology Reports*, 1(3), 87-92. <https://doi.org/10.3410/B1-87>

Kenakin, T. (2011). Functional selectivity and biased receptor signaling. *Journal of Pharmacology and Experimental Therapeutics*, 336(2), 296-302. <https://doi.org/10.1124/jpet.110.173948>

Matera, M., Page, C., & Rinaldi, B. (2018). β 2-Adrenoceptor signalling bias in asthma and COPD and the potential impact on the comorbidities associated with these diseases. *Current Opinion in Pharmacology*, 40(2), 142-146. <https://doi.org/10.1016/j.coph.2018.04.012>

Michel, M., & Alewijnse, A. (2007). Ligand-directed signalling: 50 ways to find a lover. *Molecular Pharmacology*, 72(5), 1097-1099. <https://doi.org/10.1124/mol.107.040923>

Michel, M., & Charlton, S. (2018). Biased agonism in drug discovery—Is it too soon to choose a path? *Molecular Pharmacology*, 93(4), 259-265. <https://doi.org/10.1124/mol.117.110890>

Mores, K., Cummins, B., Cassell, R., & Rijn, R. (2019). A Review of the therapeutic potential of recently developed G protein-biased kappa agonists. *Frontiers in Pharmacology*, 407(10), 10-24. <https://doi.org/10.3389/fphar.2019.00407>

Palanche, T., Ilien, B., Zoffmann, S., Reck, M., Bucher, B., Edelstein, S., & Galzi, J. (2001). The neurokinin-A receptor activates calcium and cAMP responses through distinct conformational states. *The Journal of Biological Chemistry*, 276(37), 34853-61. <https://doi.org/10.1074/jbc.M104363200>

Song, Q., Ji, Q., & Li, Q. (2018). The role and mechanism of β -arrestins in cancer invasion and metastasis (Review). *International journal of molecular medicine*, 41(2), 631-639. <https://doi.org/10.3892/ijmm.2017.3288>

Swaminath, G., Xiang, Y., Lee, T., Steenhuis, J., Parnot, C., & Kobilka, B. (2004). Sequential binding of agonists to the β 2 adrenoceptor. *Journal of Biological Chemistry*, 279(1), 686-91. <https://doi.org/10.1074/jbc.M310888200>

Whalen, E., Rajagopal, S., & Lefkowitz, R. (2010). Therapeutic potential of β -arrestin and G-protein-biased agonists. *Trends in Molecular Medicine*, 17(3), 126-139. <https://doi.org/10.1016/j.molmed.2010.11.004>

Wootten, D., Christopoulos, A., Marti-solano, M., Babu, M., & Sexton, P. (2018). Mechanisms of signalling and biased agonism in G protein-coupled receptors. *Nature Reviews*, 19(10), 638-653. <https://doi.org/10.1038/s41580-018-0049-3>

discussionsjournal@gmail.com

discussionsjournal.com/submit

**RESEARCH.
DISCOVER.
PUBLISH.**

