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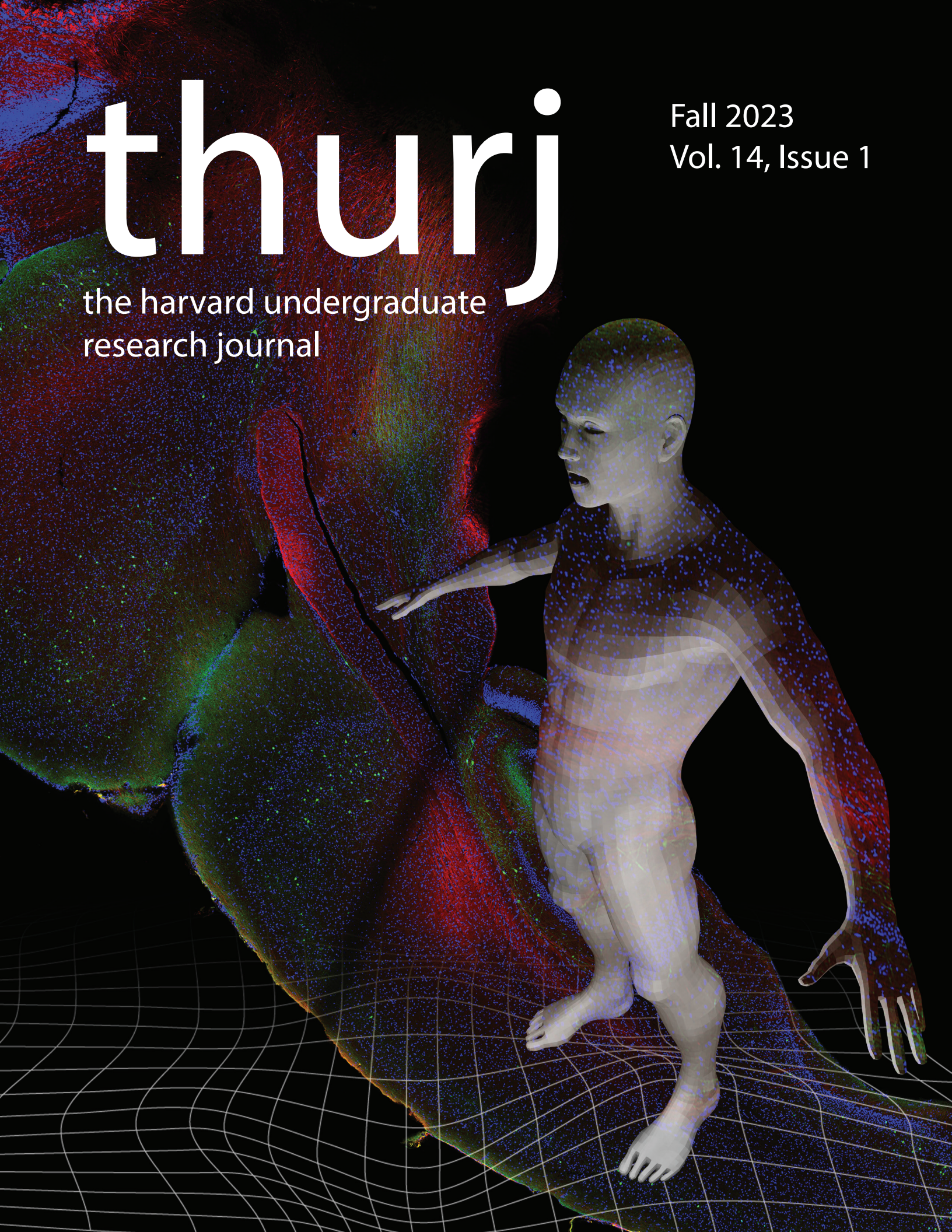

December 2023

Dear Harvard Community,

It is my pleasure to present the Fall 2023 issue of The Harvard Undergraduate Research Journal (THURJ), a student-run biannual publication dedicated to showcasing exceptional research from the Harvard undergraduate community.

THURJ was founded in 2007 with the mission of publicizing original work by Harvard undergraduates and quickly became a leading publication on the College campus. Unfortunately, like many good things, its success was short-lived—the last complete edition was published digitally in the spring of 2021, and the last print edition was published in the fall of 2019. The THURJ name has almost entirely lost its meaning among Harvard College students since then.

Luckily, thanks to past THURJ Executive Board members' unending commitment to the organization, I was able to gain access to numerous old records, including login information and layout templates. The most integral part of a student organization is its members, however, and I could not be more proud of the Fall 2023 Executive Board for their work in creating this journal. In the process of planning for this semester, I chose each individual on this Executive Board using the following criteria: 1) takes pride in their work, 2) collaborates well with other individuals, 3) demonstrates leadership qualities, 4) is both capable and knowledgeable, and 5) displays commitment to the organization. Each of these Executive Board members has exceeded my expectations, and the journal you see before you would not exist without their hard work and dedication. Reviving an organization and stepping directly into a leadership role is never easy, but they tackled each challenge head-on and with a smile.

Furthermore, this semester's General Board has been absolutely phenomenal. Their immense efforts in creating, editing, and polishing this issue are both visible and tangible, and their dedication to THURJ is greatly appreciated. Of course, we are also extremely appreciative of our faculty reviewers and advisors, who provided essential feedback that has helped us shape this journal and—more broadly—the revamped organization that THURJ is today. Last but certainly not least, I would like to thank FAS Dean of Arts and Humanities Robin Kelsey for his support in reviving THURJ.

All of us in THURJ are incredibly excited and proud to present our newest issue and to share this outstanding research with the Harvard community. Please enjoy!

Sincerely,

Ellie Shin
Editor-in-Chief

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About Us

The Harvard Undergraduate Research Journal (THURJ) showcases peer-reviewed undergraduate student research from all academic disciplines. As a biannual publication, THURJ familiarizes students with the research publication process. This process not only stimulates faculty student collaboration and provides students with valuable feedback on their research, but also promotes collaboration between the College and Harvard's many graduate and professional schools.

In addition to publishing original student research papers, THURJ keeps the Harvard community updated on and provides an important forum for discourse on the cutting-edge research that impacts our world today.

About the Cover

Alyssa Suh '25

In this captivating issue, our cover art serves as a visual symphony, intertwining the intricate map of a mouse brain with the ethereal contours of a 3D human projection. This fusion mirrors the interdisciplinary essence of our featured articles, where diverse fields converge to illuminate the uncharted territories of knowledge. The magazine extends its gratitude to Ari Cheriyan, Corey Becker, and Daniel Mhrous for generously providing the stained image of a sagittal section of a mouse brain obtained from Neuroengineering ES225.

Research

Economic Assimilation of Asian American Immigrants by Nationality: Aging and Cohort Effects, and the Model Minority Myth

Shang Wang
Harvard College '24

This paper examines the income profiles of Asian American immigrants from six major Asian countries of origin, disaggregated, relative to U.S. natives between 1970 and 2020. We observe more recent cohorts to experience either higher or similar levels of relative entry wages compared to older cohorts for all six Asian countries. Further, while the "model minority" stereotype often suggests that Asians collectively work tirelessly to achieve success, leading to smoother economic assimilation into American society compared to immigrants from other backgrounds, our findings challenge this notion. We discover that economic assimilation among immigrants from these six Asian countries of origin follows distinct patterns, and there is no overarching narrative that supports the idea of a collective "model minority" among them.

Introduction

Many labor economists have studied the wage profiles of immigrants and the convergence of these wage differentials relative to U.S. natives as a measurement of economic assimilation, with Chiswick (1978) and Borjas (2015) being the two most notable examples.

In particular, Borjas's (2015) research on the evolution of wages of all immigrants between 1970 and 2010 revealed that more recent immigrant cohorts exhibited relatively lower entry wages, and a slower rate of economic assimilation compared to earlier cohorts. In our study, we replicate Borjas's empirical methods but focus exclusively on data concerning Asian American immigrants originating from six major countries, disaggregated. We want to examine if Asian immigrants display similar trends to those observed in Borjas's overall findings.

Despite Asian immigrants arriving to parts of the U.S. since the 17th century, large-scale Asian immigration only commended in the 19th century. Furthermore, various immigration laws during the 1880s-1920s excluded many Asian immigrants from the U.S. Subsequent reforms in immigration laws during the 1940s to 1960s, which eliminated national origins quotas, led to a rapid increase in Asian immigration. As of 2020, approximately 20 million Americans identified as Asian.

According to a 2012 nationwide survey conducted by the Pew Research Center, Asian Americans today report higher satisfaction levels than the general American population regarding their lives, finances, and the country's direction (Pew Research Center 2012). Additionally, they place greater emphasis on marriage, parenthood, hard work, and career success compared to other Americans. Moreover, on average, Asian Americans outperform white natives in terms of educational attainment, intergenerational education mobility, income, occupational status, occupational mobility, and income mobility (Iceland 1999, Kao and Thompson 2003, Sakamoto et al. 2009). This is a significant departure from a century ago when most Asian Americans held low-skilled, low-wage jobs, resided in ethnic enclaves, and faced discrimination in the labor market.

Duleep and Sanders (2012) document that Asians exhibit a substantial unexplained earnings gap in 1960 that largely vanishes by 1980, and suggest that this change likely relates to Civil Rights legislation. Additionally, conventional wisdom attribute Asian immigrants' success to the "model minority" stereotype, that despite facing obstacles such as discrimination related to citizenship, due process, and legal rights, Asian immigrants work diligently to achieve success and assimilate into American society (Kuo 1998, Kwon 2011, Lee 2015, Lew-Williams 2018).

This paper examines the income profiles of Asian immigrants from six major Asian countries of origin, disaggregated, to assess whether the "model minority" myth is reflected as a prevailing trend among them. In addition to studying the assimilation rate over time between countries, we also explore the assimilation rate between cohorts over time within each country.

Methods

Data

We analyze the income profiles of Asian immigrants from China, India, the Philippines, Korea, Vietnam, and Japan. In our classification, "immigrants" encompass individuals who are born in any of the six Asian countries, irrespective of whether they later became naturalized citizens in the U.S. On the other hand, we designate "natives" as white males born in any of the 50 U.S. states.

Our dataset comprises all available decennial census data spanning from 1970 to 2000, as well as the pooled 2009-2011 and 2019-2021 American Community Surveys (ACS). The ACS is currently the largest available survey that includes information on race/ethnicity and socioeconomic characteristics. For simplicity, we refer to the pooled 2009-2011 and 2019-2021 ACS survey data as 2010 and 2020 censuses, respectively.

As is customary in labor force studies, we limit our native and immigrant sample to male adults of working age (18 to 65). We also restrict our immigrant sample exclusively to males who immigrated to the U.S. after turning 18 to ensure the tracking of cohorts across censuses is unaffected by subsequent waves of

immigrants who arrive as children. This accounts for the possibility that immigrant children likely assimilate faster than their adult counterparts due to their integration into the American education system.

Regression Equations

We estimate the following regression model in each of the census cross-sections from 1970 to 2020 and for each country of origin.

$$log\ (wage)_{itc} = \Phi_{ct} + X_{it}\beta_t + u_{itc}$$

The dependent variable is the logarithm of the total pre-tax wage and salary income earned by a worker i in cross-section t and in cohort c compared to natives. The regressors include the worker's age introduced as a third-degree polynomial, X_{it}.

Φ_{ct} are the fixed effects of a specific cohort in a given cross-section. We also control for education, which represents the observable differences in skills between Asian immigrants and natives. Finally, the regression model includes a fixed effect for the immigrant cohort that arrived on or before 1949 so that the earliest cohort starts at 1950.

Main Results

Tables 1-6 display regression coefficients for all six Asian countries. In contrast to Borjas's (2015) findings, where he observed that immigrants of all races and ethnicities in more recent cohorts had relatively lower entry wages compared to earlier cohorts, our study reveals a different trend among Asian immigrant cohorts. Specifically, we find that more recent Asian immigrant cohorts tend to experience either improved or similar levels of initial wage disadvantage upon entry compared to older cohorts for all six Asian countries.

For example, when we control for age and education, Chinese immigrants who arrived in 1965 and 1975 earned approximately 70% less than natives during their first decade in the U.S. However, Chinese immigrants who arrived in 2005 earned around 50% less than natives, and this wage gap was further reduced to approximately 30% for the latest wave of Chinese immigrants arriving in 2015. This indicates an improvement in the initial wage disadvantage over time. Similarly, Indian immigrants experienced an initial wage disadvantage of around 50-60% compared to natives for the 1965 and 1975 cohorts, but this gap diminished with each subsequent cohort and eventually closed entirely by 2020. On the other hand, Filipino immigrants exhibited a relatively stable pattern, starting with the 1965 and 1975 cohorts earning around 50-60% less than natives upon arrival, and this wage disadvantage persisted in successive cohorts, plateauing at around 48-53% in 2005 and 2015. In contrast, Korean immigrants from the 1975 to 2005 cohorts had a wage gap of approximately 60% relative to natives, which reduced to around 40% in 2015, indicating a modest level of improvement relative to earlier cohorts. These examples either contradict Borjas's findings on lower entry wages for immigrants overall or demonstrate no significant changes in the long-term trend of entry wages for specific Asian countries.

Table 1: Age-adjusted relative earnings of Chinese immigrant cohorts by census cross sections

VARIABLES	(1) 1970 Relative Weekly Earnings	(2) 1980 Relative Weekly Earnings	(3) 1990 Relative Weekly Earnings	(4) 2000 Relative Weekly Earnings	(5) 2010 Relative Weekly Earnings	(6) 2020 Relative Weekly Earnings
1950-1959 arrivals	-0.257***	-0.143***	0.121***	0.267***		
	(0.000)	(0.000)	(0.000)	(0.001)		
1960-1964 arrivals	-0.389***	-0.146***	0.000***	0.048***	-0.084***	
	(0.000)	(0.000)	(0.000)	(0.001)	(0.001)	
1965-1969 arrivals	-0.686***	-0.299***	-0.077***	0.068***	-0.121***	
	(0.000)	(0.000)	(0.000)	(0.001)	(0.000)	
1970-1974 arrivals		-0.426***	-0.203***	-0.039***	0.134***	-2.130***
		(0.000)	(0.000)	(0.001)	(0.000)	(0.001)
1975-1979 arrivals		-0.733***	-0.339***	-0.254***	0.090***	-0.115***
		(0.000)	(0.000)	(0.001)	(0.001)	(0.004)
1980-1984 arrivals			-0.405***	-0.238***	-0.084***	-0.256***
			(0.000)	(0.001)	(0.001)	(0.002)
1985-1989 arrivals			-0.867***	-0.291***	-0.097***	0.090***
			(0.000)	(0.000)	(0.000)	(0.001)
1990-1994 arrivals				-0.330***	-0.149***	0.000***
				(0.000)	(0.000)	(0.001)
1995-1999 arrivals				-0.617***	-0.142***	-0.062***
				(0.001)	(0.000)	(0.001)
2000-2004 arrivals					-0.284***	-0.095***
					(0.000)	(0.000)
2005-2009 arrivals					-0.514***	-0.109***
					(0.000)	(0.001)
2010-2014 arrivals						-0.055***
						(0.002)
2015-2019 arrivals						-0.326***
						(0.003)
Observations	39,583,700	46,182,420	48,990,278	250,286,844	151,335,121	145,603,530
R-squared	0.364	0.298	0.344	0.333	0.368	0.324

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 2: Age-adjusted relative earnings of Indian immigrant cohorts by census cross sections

VARIABLES	(1) 1970 Relative Weekly Earnings	(2) 1980 Relative Weekly Earnings	(3) 1990 Relative Weekly Earnings	(4) 2000 Relative Weekly Earnings	(5) 2010 Relative Weekly Earnings	(6) 2020 Relative Weekly Earnings
1950-1959 arrivals	0.077***	0.147***	0.359***	0.121***		
	(0.000)	(0.000)	(0.000)	(0.001)		
1960-1964 arrivals	-0.122***	0.201***	0.271***	0.330***	0.185***	
	(0.000)	(0.000)	(0.000)	(0.001)	(0.001)	
1965-1969 arrivals	-0.660***	0.113***	0.232***	0.393***	0.217***	
	(0.000)	(0.000)	(0.000)	(0.001)	(0.001)	
1970-1974 arrivals		-0.067***	0.156***	0.214***	0.289***	0.062***
		(0.000)	(0.000)	(0.000)	(0.000)	(0.004)
1975-1979 arrivals		-0.510***	-0.018***	0.141***	0.305***	0.104***
		(0.000)	(0.000)	(0.000)	(0.001)	(0.002)
1980-1984 arrivals			-0.143***	-0.070***	0.131***	0.248***
			(0.000)	(0.000)	(0.001)	(0.001)
1985-1989 arrivals			-0.543***	-0.045***	0.085***	0.264***
			(0.000)	(0.001)	(0.000)	(0.001)
1990-1994 arrivals				0.013***	0.123***	0.276***
				(0.002)	(0.001)	(0.001)
1995-1999 arrivals				-0.102***	0.163***	0.330***
				(0.002)	(0.002)	(0.002)
2000-2004 arrivals					0.108***	0.277***
					(0.003)	(0.002)
2005-2009 arrivals					-0.047***	0.219***
					(0.003)	(0.003)
2010-2014 arrivals						0.262***
						(0.003)
2015-2019 arrivals						0.023***
						(0.005)
Observations	39,567,900	46,191,020	49,016,672	250,950,602	152,111,083	146,955,601
R-squared	0.364	0.298	0.345	0.333	0.369	0.328

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 3: Age-adjusted relative earnings of Filipino immigrant cohorts by census cross sections

VARIABLES	(1) 1970 Relative Weekly Earnings	(2) 1980 Relative Weekly Earnings	(3) 1990 Relative Weekly Earnings	(4) 2000 Relative Weekly Earnings	(5) 2010 Relative Weekly Earnings	(6) 2020 Relative Weekly Earnings
1950-1959 arrivals	-0.396***	-0.218***	0.068***	0.168***		
	(0.000)	(0.000)	(0.001)	(0.001)		
1960-1964 arrivals	-0.232***	-0.198***	-0.024***	-0.039***	-0.537***	
	(0.000)	(0.000)	(0.001)	(0.001)	(0.000)	
1965-1969 arrivals	-0.607***	-0.193***	-0.062***	-0.050***	0.096***	
	(0.000)	(0.000)	(0.001)	(0.001)	(0.000)	
1970-1974 arrivals		-0.217***	-0.092***	-0.028***	0.043***	-0.051***
		(0.000)	(0.001)	(0.001)	(0.001)	(0.001)
1975-1979 arrivals		-0.519***	-0.189***	-0.215***	-0.042***	-0.115***
		(0.000)	(0.000)	(0.001)	(0.001)	(0.001)
1980-1984 arrivals			-0.274***	-0.267***	-0.180***	-0.050***
			(0.000)	(0.001)	(0.001)	(0.001)
1985-1989 arrivals			-0.523***	-0.350***	-0.200***	-0.126***
			(0.000)	(0.000)	(0.001)	(0.001)
1990-1994 arrivals				-0.375***	-0.305***	-0.179***
				(0.000)	(0.001)	(0.001)
1995-1999 arrivals				-0.552***	-0.311***	-0.229***
				(0.000)	(0.000)	(0.001)
2000-2004 arrivals					-0.388***	-0.291***
					(0.000)	(0.001)
2005-2009 arrivals					-0.532***	-0.319***
					(0.000)	(0.000)
2010-2014 arrivals						-0.350***
						(0.000)
2015-2019 arrivals						-0.487***
						(0.000)
Observations	39,586,200	46,228,260	49,062,487	250,515,139	151,283,178	145,207,857
R-squared	0.364	0.297	0.344	0.332	0.367	0.323

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 4: Age-adjusted relative earnings of Korean immigrant cohorts by census cross sections

VARIABLES	(1) 1970 Relative Weekly Earnings	(2) 1980 Relative Weekly Earnings	(3) 1990 Relative Weekly Earnings	(4) 2000 Relative Weekly Earnings	(5) 2010 Relative Weekly Earnings	(6) 2020 Relative Weekly Earnings
1950-1959 arrivals	-0.407***	0.136***	0.417***	-0.266***		
	(0.000)	(0.000)	(0.001)	(0.001)		
1960-1964 arrivals	-0.339***	0.060***	0.231***	0.313***	0.825***	
	(0.000)	(0.000)	(0.000)	(0.001)	(0.001)	
1965-1969 arrivals	-1.184***	-0.123***	0.239***	0.432***	0.504***	
	(0.000)	(0.000)	(0.000)	(0.001)	(0.001)	
1970-1974 arrivals		-0.309***	0.006***	-0.090***	0.176***	-0.083***
		(0.000)	(0.000)	(0.000)	(0.001)	(0.001)
1975-1979 arrivals		-0.638***	-0.184***	-0.258***	0.006***	-0.049***
		(0.000)	(0.000)	(0.000)	(0.000)	(0.001)
1980-1984 arrivals			-0.299***	-0.284***	0.066***	-0.123***
			(0.000)	(0.000)	(0.000)	(0.001)
1985-1989 arrivals			-0.685***	-0.358***	-0.225***	-0.264***
			(0.000)	(0.000)	(0.000)	(0.000)
1990-1994 arrivals				-0.492***	-0.324***	-0.242***
				(0.000)	(0.000)	(0.000)
1995-1999 arrivals				-0.671***	-0.409***	-0.203***
				(0.000)	(0.000)	(0.000)
2000-2004 arrivals					-0.422***	-0.268***
					(0.000)	(0.000)
2005-2009 arrivals					-0.578***	-0.202***
					(0.000)	(0.000)
2010-2014 arrivals						-0.329***
						(0.000)
2015-2019 arrivals						-0.414***
						(0.000)
Observations	39,553,200	46,154,680	48,944,893	249,678,104	150,780,494	144,716,878
R-squared	0.364	0.298	0.344	0.332	0.367	0.324

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 5: Age-adjusted relative earnings of Vietnamese immigrant cohorts by census cross sections

VARIABLES	(1) 1970 Relative Weekly Earnings	(2) 1980 Relative Weekly Earnings	(3) 1990 Relative Weekly Earnings	(4) 2000 Relative Weekly Earnings	(5) 2010 Relative Weekly Earnings	(6) 2020 Relative Weekly Earnings
1950-1959 arrivals		0.270***	0.020***	0.292***		
		(0.000)	(0.001)	(0.001)		
1960-1964 arrivals	-0.425***	-0.622***	0.174***	0.118***		
	(0.000)	(0.000)	(0.000)	(0.001)		
1965-1969 arrivals	-1.128***	-0.096***	-0.134***	0.667***	0.987***	
	(0.000)	(0.000)	(0.000)	(0.001)	(0.001)	
1970-1974 arrivals		-0.205***	-0.044***	0.085***	0.425***	0.373***
		(0.000)	(0.000)	(0.001)	(0.000)	(0.001)
1975-1979 arrivals		-0.502***	-0.128***	-0.189***	0.140***	0.047***
		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
1980-1984 arrivals			-0.293***	-0.189***	-0.026***	0.048***
			(0.000)	(0.000)	(0.001)	(0.001)
1985-1989 arrivals			-0.549***	-0.232***	-0.111***	0.020***
			(0.000)	(0.000)	(0.001)	(0.001)
1990-1994 arrivals				-0.312***	-0.203***	-0.157***
				(0.000)	(0.001)	(0.001)
1995-1999 arrivals				-0.370***	-0.289***	-0.184***
				(0.000)	(0.001)	(0.001)
2000-2004 arrivals					-0.398***	-0.321***
					(0.001)	(0.001)
2005-2009 arrivals					-0.548***	-0.282***
					(0.001)	(0.001)
2010-2014 arrivals						-0.239***
						(0.001)
2015-2019 arrivals						-0.441***
						(0.001)
Observations	39,545,600	46,156,940	48,971,733	250,319,935	150,994,296	144,935,524
R-squared	0.364	0.298	0.344	0.332	0.367	0.324

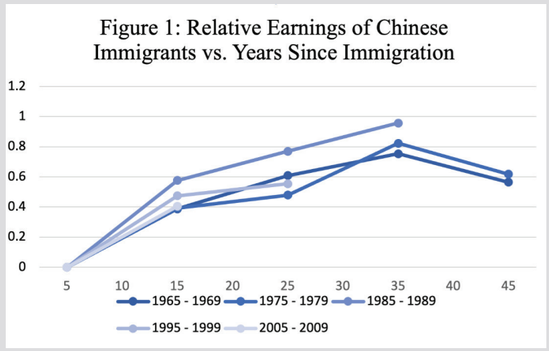
Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

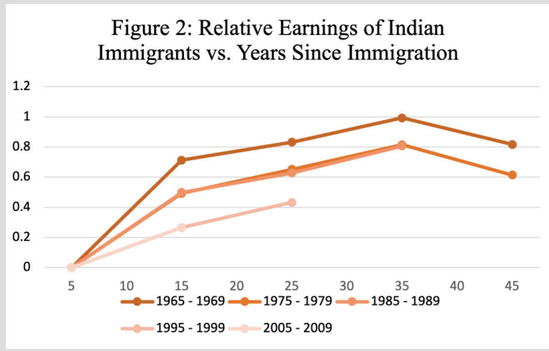
Table 6: Age-adjusted relative earnings of Japanese immigrant cohorts by census cross sections

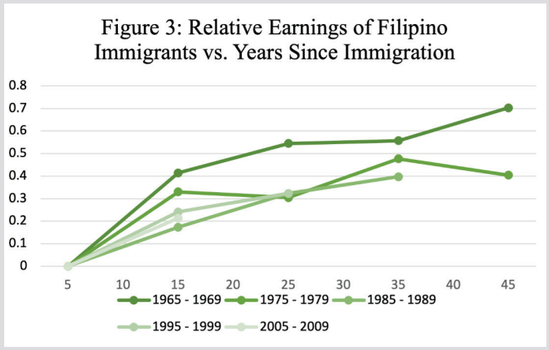
VARIABLES	(1) 1970 Relative Weekly Earnings	(2) 1980 Relative Weekly Earnings	(3) 1990 Relative Weekly Earnings	(4) 2000 Relative Weekly Earnings	(5) 2010 Relative Weekly Earnings	(6) 2020 Relative Weekly Earnings
1950-1959 arrivals	-0.214***	0.055***	0.290***	0.445***		
	(0.000)	(0.000)	(0.000)	(0.000)		
1960-1964 arrivals	-0.210***	0.015***	0.355***	0.125***	0.707***	
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	
1965-1969 arrivals	-0.498***	-0.069***	0.254***	0.316***	0.154***	
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	
1970-1974 arrivals		-0.109***	-0.028***	0.123***	-0.329***	-0.848***
		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
1975-1979 arrivals		-0.094***	-0.014***	0.129***	-0.086***	0.156***
		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
1980-1984 arrivals			0.096***	-0.017***	-0.110***	-0.060***
			(0.000)	(0.000)	(0.000)	(0.000)
1985-1989 arrivals			0.222***	0.021***	-0.013***	0.096***
			(0.000)	(0.000)	(0.000)	(0.000)
1990-1994 arrivals				0.082***	-0.116***	0.066***
				(0.000)	(0.000)	(0.000)
1995-1999 arrivals				0.173***	0.033***	-0.030***
				(0.000)	(0.000)	(0.000)
2000-2004 arrivals					0.018***	0.138***
					(0.000)	(0.000)
2005-2009 arrivals					0.193***	-0.000***
					(0.000)	(0.000)
2010-2014 arrivals						0.226***
						(0.000)
2015-2019 arrivals						0.187***
						(0.000)
Observations	39,557,700	46,140,900	48,923,820	249,430,678	150,513,044	144,459,988
R-squared	0.364	0.298	0.344	0.333	0.368	0.324

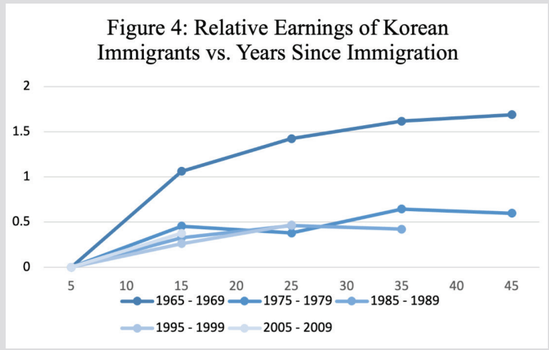
Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

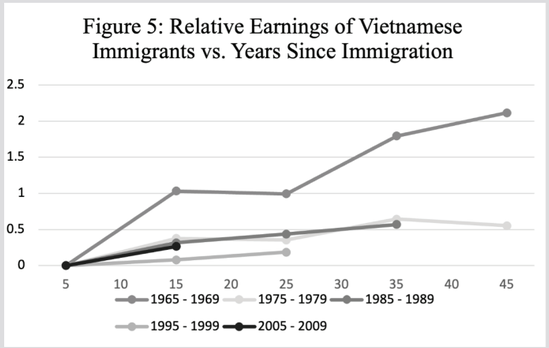
Table 1-6: Aging profile for relative wage of immigrants, by cohort and by country. The aging profiles are obtained from the data reported in Tables 1-6, respectively. The relative log wage of each immigrant cohort is normalized to zero at the time of entry for each country.

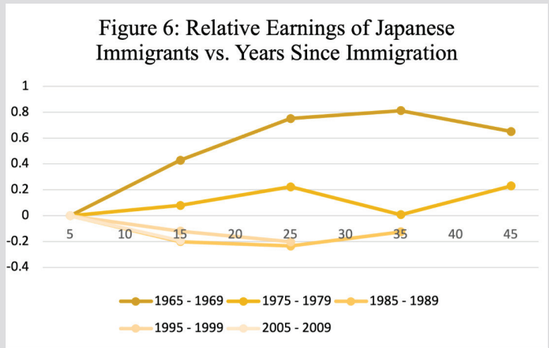












Next, we define the rate of economic assimilation as the pace at which the wage gap between migrants and natives narrows over time. In contrast to Borjas's (2015) findings on the slowdown of assimilation rates in successive cohorts over time for immigrants of all origins (referred to as "cohort effects"), we find no substantial evidence of this collective assimilation pattern in successive cohorts for all six Asian countries.

For instance, when examining Korean and Japanese immigrants, we observe that the wage differential relative to natives for the 1950-1975 cohorts closed within their first decade upon arrival in the U.S., but it did not close as rapidly for subsequent cohorts within the first decade. Similarly, all Indian cohorts experienced rapid assimilation, with the wage gap closing for each cohort within their first five or ten years in the U.S. In contrast, Chinese immigrants experienced slower rates of assimilation, as seen in the 1950 and 1960 cohorts, where their wages were, on average, at a disadvantage of around 25.7% and 38.9%, respectively, compared to their native counterparts. This wage gap closed, as demonstrated in the 1990 and 2000 censuses, respectively, after 40 years of their residence in the U.S. Likewise, Vietnamese cohorts generally experienced much slower assimilation, with the wage gap closing for each cohort after 40 years of residency in the U.S.

While the analyses above focus on the rate of assimilation over time between different countries, figures 1-6 show the rate of assimilation between cohorts within a single country across time. We have normalized the wages for each cohort so that the logarithm of the wage at the time of entry is 0, thereby capturing the cohort effects and allowing us to visualize how cohorts evolve over time.

When examining the graphs for Indian, Filipino, Korean, Vietnamese, and Japanese immigrants, a general trend emerges where older cohorts tend to exhibit a higher rate of assimilation. However, in contrast, the graph for Chinese immigrants reveals that more recent cohorts experience a greater rate of assimilation.

In summary, immigrant cohorts from each Asian country display unique and divergent trends, indicating the absence of any clear, uniform pattern. This finding contradicts the "model minority" myth that suggests a consistent pattern of success among Asian immigrant cohorts.

Discussion

Within our data, we find that more recent Asian immigrant cohorts experience either higher or similar levels of relative wages upon entry compared to older cohorts for all six Asian countries. We also find no uniform pattern of rates of assimilation in cohorts for all six Asian countries, contradicting the "model minority" myth.

Perhaps the most obvious explanation for the wage gap between immigrants and natives is that immigrant and native populations have a different mix of skill sets. The observed skill-based differences would be in education, and the unobserved skill-based differences would be discrimination in the labor market, English language barriers, and more. Another aspect of unobserved skill differences (or omitted variable bias) in the measurement of skill could be that educational attainment in foreign countries may not completely transfer into the U.S. (for instance, cultural differences in the workplace, additional licensing needed for the corresponding field in the U.S., etc.) that cause an immigrant to be unable to obtain a job that matches his or her qualification as their U.S. native counterparts.

Conclusion

This paper utilizes data drawn from the 1970–2000 decennial U.S. censuses and pooled 2009-2011 and 2019-2021 ACS data to document and investigate the long-run trends in Asian immigrant earnings spanning several decades, disaggregated by country of origin. One of the central findings of this paper is that, on average, more recent cohorts of Asian American immigrants tend to experience either higher or similar levels of entry wages compared to natives. Furthermore, the long-term trends in the data question the validity of the "model minority" myth, which assumes that all Asian American descendants uniformly outperform U.S. natives, as we observe very distinct paths in the economic assimilation of various Asian groups.

However, this study has a notable limitation, namely, we assumed that immigrants from earlier censuses continue to be present in successive censuses in order to track cohorts over time. In reality, individuals may retire, pass away, or simply return to their home countries, which is more likely for those who may have faced unfavorable job prospects in the U.S. This could lead to an underestimation of the true economic progress within a cohort. Therefore, it is imperative to replicate these findings using longitudinal samples rather than relying solely on the repeated cross-sectional data available in census records. While tracking individual immigrants across several decades may be logistically challenging, it would enhance the validity of our results.

Furthermore, it is essential to account for inflation when assessing earnings growth to obtain a comprehensive understanding of assimilation within a cohort. Macroeconomic conditions can also introduce biases into estimates of aging and cohort effects. Events like the Cold War, the Dot Com Bubble, or the 2008 Great Financial Crisis, may disproportionately impact specific groups of immigrants. It is probable that the variation in how these groups are impacted before and after a certain event is similar, and our cross-sectional methodology effectively captures this effect. However, in future research, we can evaluate whether all groups are equally affected by measuring their correlation with macro events.

Finally, our study samples are restricted to Asian immigrants from the six major countries of origin, which means that smaller Asian countries are not included in our analysis. A more comprehensive analysis is required to precisely gauge the impact of these factors on the wage assimilation patterns over time for all Asian immigrant groups.

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Qualitative Histopathological Analysis of Bleomycin-Induced Lung Injury

Emily Gao
Harvard College '26

Recent evidence has suggested that the accumulation of cholesterol-laden "fatty macrophages" in the lung may play a key role in the presentation of ALI 1, a condition that affects nearly 200,000 people per year in the United States. Studying the pathways of these cells suggests that preventing the formation and build-up of these macrophages could prevent many of the characteristic symptoms of acute lung injury. Specifically, this experiment aims to explore the effect that ACAT1 inhibition by K604 has on fatty macrophage formation and outcomes of ALI. To test this, different groups of mice were administered either PBS (as control), ITB (intratracheal bleomycin), PBS + K604, or ITB + K604. After the mice were sacrificed, the left lung lobes were extracted, inflated, embedded, and sectioned for microscopic scanning and analysis with the ImageJ software. The lung tissue was characterized using 3 unbiased parameters: alveolar wall thickness (μm), cell infiltration (number of nuclei), and percent white space. Simultaneously, a cholesterol assay was performed using cells extracted from mouse bronchoalveolar lavage (BAL). The results show that K604 was successful at preventing ITB-induced increases in cell infiltration, consolidation, and alveolar thickening as well as lipid accumulation in macrophages by limiting the formation of cholesterol esters through ACAT1 inhibition. In this respect, this experiment shows that K604 might be a viable pharmaceutical target in the treatment of ALI.

Introduction

Acute lung injury (ALI) is a condition primarily characterized by inflammation, thickening of alveolar walls, and immune cell invasion. Currently, options for pharmaceutical treatments for acute lung injury are scarce 2, and most could be categorized as "physical" (such as mechanical ventilation or fluid management). Unfortunately, these treatments often have their own drawbacks that could lead to further deterioration in patients, so more focus is currently being placed on discovering more viable and long-term pharmaceutical solutions.

Many of the symptoms found during ALI are primarily driven by macrophages, as errors in macrophage activation or function can exacerbate the damages brought upon by ALI. One of the most pressing issues revolves around the dysregulation of lipid homeostasis [1] in macrophages. Under normal circumstances, cholesterol is excreted from macrophages and out of the cells through active transport, but with ALI, the macrophages are overwhelmed, leading to an accumulation of what is often termed "fatty macrophages" 1. The build-up of these macrophages results in more lipid and cholesterol accumulation in the cells, causing further damage to the lung.

More specifically, when cholesterol levels in macrophages are high, increased esterification occurs in the cell with the help of the mitochondrial enzyme ACAT1 (acetyl-CoA acetyltransferase 1), leading to a conversion from cholesterol to cholesterol esters 1. This process is regarded as integral to lipid droplet formation in the cells and contributes to the formation of fatty macrophages. However, it was discovered that K604 (a specific acyl-CoA:cholesterol acyltransferase 1 inhibitor) could prevent ACAT1 from functioning by acting as a competitive inhibitor of the mitochondrial enzyme 3, and in turn, halt the formation of cholesterol esters 4. Since it is strongly believed that the presence of fatty macrophages is a major contributing factor behind injury in ALI and that the accumulation of these macrophages is a direct result of the creation of cholesterol esters 5, this experiment attempted to explore the extent of the effectiveness of inhibiting ACAT1 through an unbiased method in assessing the degree of lung injury driven by cholesterol-laden macrophages in ALI.

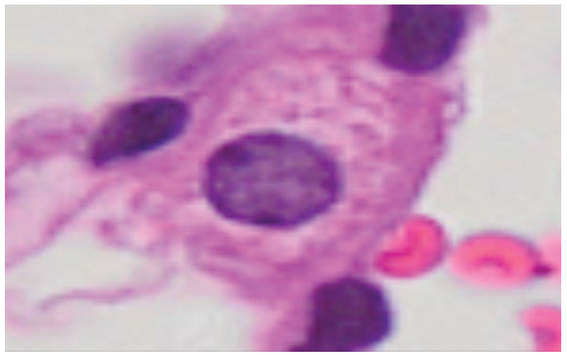

Fig. 1: "Fatty" macrophages with great lipid and cholesterol accumulation. (represented by light purple buildup)

Healthy and fully functioning macrophages are essential to effective injury response and repair during ALI. Macrophages are considered the "first line of defense" against pathogens and release substances into the lungs that will help give rise to a stronger inflammatory response. In this experiment, intratracheal-bleomycin was administered directly to the mice to simulate acute lung injury; specifically, ITB causes the mice to exhibit some main features of ALI that are studied in this experiment, including an increase in neutrophils in BALF (50-60%), pulmonary edema, and lung pathology6. K604 was also similarly administered directly through the lungs.

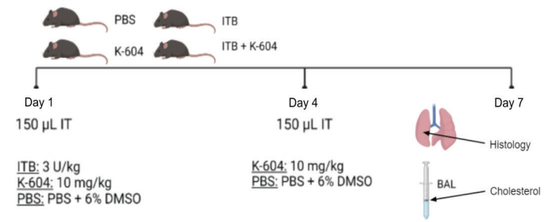

Fig. 2: Timeline of experimental design. Histology and cholesterol occur on Day 7.

Methods

Animal Use

Both male and female wild-type C57BL6/J mice (6-8 weeks old) were obtained from Jackson Laboratories (Bar Harbor, ME, USA) and housed in groups of 4 per cage (separated by sex) under standard conditions; they were provided food and water ad libitum and received humane care in compliance with Rutgers University IACUC-approved protocols adhering to the NIH guidelines for the care and use of laboratory animals 7. Equal numbers of male and female mice were used, even though males are traditionally more susceptible to ALI and its symptoms 8. The mice were treated with either PBS, intratracheal bleomycin, K604, or both ITB and K604 throughout the experiment; all were sacrificed seven days after initial intratracheal administration of K604 or bleomycin (Santa Cruz, Cat# sc-200134B).

K604 and Bleomycin Administration

The mice were first anesthetized with isoflurane and received a single intratracheal administration of either 50 uL PBS, 10 mg/kg K604, 3 U/kg bleomycin, or 10 mg/kg K604 + 3U/kg bleomycin. All volumes were brought up to 150 uL with 6% DMSO (dimethyl sulfoxide). The mice were observed to fully ensure that the complete dose was correctly administered and that the mice recovered from the anesthesia. 72 hours later, the mice were re-anesthetized and administered 50 uL PBS or 10 mg/kg K604 (intratracheally).

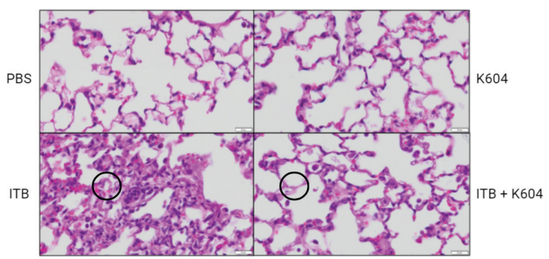

Fig. 3: Representative histopathological images from each condition, based on the average of 10 areas. Images were captured from both males and females from all four groups. The healthiness of the lung was determined by 3 parameters: alveolar wall thickness, cell infiltration (number of nuclei), and percent white space. The bottom right analysis shows a significantly healthier condition as the ITB-treated mice were administered the K604 treatment: on the other hand, as seen in the bottom left, all 3 parameters point towards unhealthy ALI symptoms.

The mice were sacrificed seven days after initial intratracheal administration.

BAL Cell Cholesterol Quantitation

After sacrificing the mice, 10,000 to 20,000 cells were extracted from the BAL fluid for cholesterol analysis. The concentration of total cholesterol, free cholesterol, and cholesterol esters in the BAL cell samples were all measured. A bioluminescent Cholesterol/Cholesterol Ester-Glo™ Assay (Promega, Madison, WI) was utilized and luminescence was recorded on a SpectraMax®M2 multi-mode microplate reader (Molecular Devices, San Jose, CA) utilizing SoftMax Pro software v5.3.

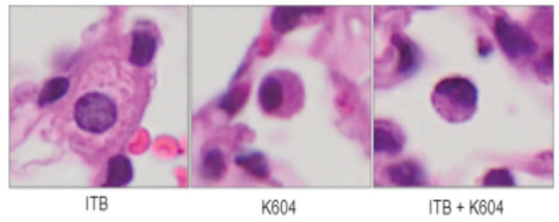

Fig. 4: Very large macrophages such as the one in the far left are often observed in the fluid of ITB-treated mice, leading to lipid accumulation in the lungs. On the other hand, administration of K-604 to ITB-treated mice appears to reduce the number of large macrophages in the cells when compared to ITB alone. Even in mice not treated with ITB, K604 has no negative effects on macrophage growth, as seen in the middle image.

Histology

After the BAL fluid collection, the large left lung lobe was extracted, inflated, fixed in paraformaldehyde (3%), and embedded in paraffin. Sections of 4 uM were stained with hematoxylin and eosin for histopathological analysis. Each slide was scanned at 40x

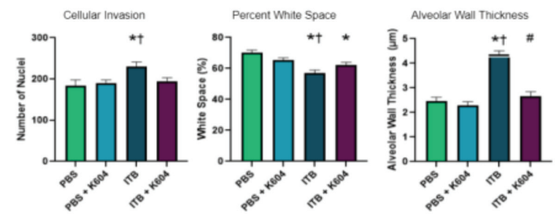

Fig. 5: Administering ITB increases the degree of cellular invasion (more nuclei), decreases the percent white space, and increases average alveolar wall thickness. On the other hand, treating with K604 seems to mitigate all three of these symptoms, directing them back toward the direction of the control and K604 specimens.

with the VS120 Virtual Slide Microscope (Olympus, Waltham, MA) and viewed under the OlyVIA viewing software for virtual slide images (Olympus). From each histological slide, 10 randomly chosen areas were captured and analyzed to determine the healthiness of the lung through 3 parameters: average alveolar wall thickness, cell infiltration (number of nuclei), and tissue consolidation (percent of open white tissue space) using ImageJ. These parameters were picked specifically to observe the impact and prevalence of described "fatty macrophages." After all data

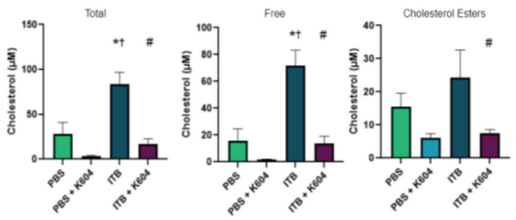

Figure 6: ITB increases the amount of total cholesterol, free cholesterol, and cholesterol esters (per 1 x 104 cells). Total cholesterol (83.59±13.26 vs 27.82±13.17) and free cholesterol (72.63±11.68 vs 15.51±9.11) are increased in BAL macrophages compared to control. Compared to ITB alone, co-administration of K604 mitigates the increase in total cholesterol (16.94±5.71 vs 83.59±13.26), free cholesterol (13.79±5.4 vs 71.63 ±11.68), and cholesterol esters (7.45±1.19 vs 24.23±8.39). Data are representative of 3 separate experiments, where n=5-16 per group. $p < 0.05$ when compared with PBS (*), PBS + K604 (†), and ITB (#).

was collected and recorded, the Prism software was used to consolidate all numbers into graphs.

Results/Discussion

Data gathered from the experiment successfully demonstrated that ACAT1 inhibition may be a viable target to improve the condition of the lung in ALI by maintaining a healthy macrophage status. With reduced levels of cholesterol, both free and esters, the macrophages had a much smaller chance of turning "fatty" and consequently the lungs showed signs of improvement across all three measured parameters (alveolar wall thickness, cell infiltration, and percent white space).

Preliminary observations of the histological cells in ImageJ displayed general trends across the four groups of mice: PBS (control), ITB (intratracheal bleomycin), K604 (only the ACAT1 inhibitor), and ITB + K604 (intratracheal bleomycin and the inhibitor). Administration of ITB led to thickening of the alveolar walls across the entire area, simulating ALI (Figure 3). The average alveolar cell wall length is notably thicker in the ITB group than all other three groups, including the treated mice. Concurrently, there seemed to be a much higher degree of immune cell invasion in the ITB group compared to the others.

The three parameters that were used to measure the healthiness of an area of the lung were: average alveolar wall thickness, cell infiltration, and percent white space. Optimally, a healthy lung would look very similar to the control lung shown in Figure 3: thin but reasonably sized walls, an average number of nuclei proportional to the space covered, and a generous percent of white space. In this respect, it can also be seen that the K604 treatment alone has no negative effects on the condition of the lung; the second group administered just K604 appeared as healthy as the control. Even more interestingly, the mice that were administered ITB but also treated with K604 showed promising signs of improvement in regard to all three parameters.

Zooming into the histological images, the difference in the state of the macrophages can be observed between the three experimental groups. Figure 4 shows how varying "types" of macrophages appear based on the level of cholesterol accumulation. "Fatty macrophages" (or large macrophages, categorized as diameter > 8 μm) were observed much more often in the ITB-administered mice compared to the control or K604-treated mice, further indicating that K604 seems to have very visible benefits for the state of the lung.

More concretely, the graphs in Figure 5 numerically illustrate the benefits of K604 administration to the mice in all three parameters. The ITB + K604 mice generally had reduced cellular infiltration (1.94.94 +/- 2.20 vs 229.72 +/- 3.318), a higher percent of white space (62.34 +/- 0.42% vs 57.04 +/- 0.54 %), and less severe alveolar wall thickening (2.66 +/- 0.05 vs 4.35 +/- 0.04) compared to the ITB alone animals. Therefore, K604 was helpful in preserving the condition of the macrophages by preventing cholesterol buildup, which in turn assists in maintaining the health of the entire lung. Additionally, the conditions of the ITB + K604 mice seemed to be almost similar to the control and K604-only mice with regards to all three characteristics.

In addition to maintaining the average alveolar wall thickness, cell infiltration, and percent white space to reasonable values similar to healthy control mice, K604 is also observed to reduce the formation and build-up of cholesterol esters directly. As shown in Figure 6, the ITB+K604 animals have lower levels of total cholesterol, free cholesterol, and cholesterol esters compared to the ITB animals. Through utilizing the Cholesterol/Cholesterol Ester-GloTM Assay kit (Promega©) and extracting cells from the BAL fluid, it can be seen that administering ITB significantly increases levels of all cholesterol in the cells and lungs, henceforth explaining the accumulation of "fatty macrophages" observed in the histological images. On the other hand, with K604 administration, cholesterol levels were very noticeably lower (total: 16.94±5.71 vs 83.59±13.26, free: 13.79±5.4 vs 71.63 ±11.68, cholesterol esters: 7.45±1.19 vs 24.23±8.39). This reduction suggests that K604 prevents cholesterol accumulation.

Thus, based on collected data, ACAT1 inhibition, by K604 or a similar compound, could be considered as a viable treatment option for ALI.

Conclusion

In closing, this experiment aimed to determine the effectiveness of inhibiting ACAT1, through K604, on the formation of fatty macrophages in ALI. The results were promising, as the data demonstrates that the K604 was effective in preventing both cholesterol ester formation and accumulation of fatty macrophages. In turn, this development led to generally healthier lungs, as observed under ImageJ, with values for alveolar cell wall thicknesses, number of nuclei, and percent white space returning closer to the values observed in the control animals. The data shows that K604 could be a realistic pharmaceutical treatment for acute lung injury, especially since there is a current lack of this in regards to ALI; however, given that this is a newer idea, further experimentation must be performed to investigate any underlying mechanisms and potential side effects of this ACAT1 inhibition. Ultimately, with more robust (and less fatty) macrophages, there could be a much stronger line of defense in the lung in response to pathogens involved in ALI, and thus protect patients against this condition to a much better degree.

This research was conducted at the Ernest Mario School of Pharmacy with Emily Stevenson and Dr. Andrew Gow.

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Features

Are We Alone? One Question, One Scientist, Two Harvard Initiatives

Harvard Astronomy professor (right) and his research team embarked on an expedition from June 14 to June 28 to retrieve materials from the first interstellar meteor, IM1. Photo courtesy of Avi Loeb.

Andrés Muedano Sosa ‘27

In the vast expanse of the universe, humanity has long pondered one fundamental question: are we alone? Historically, the search for extraterrestrial life has focused on the passive detection of electromagnetic signals from distant starts. However, Professor Abraham “Avi” Loeb, leader of Harvard’s Galileo Project, has taken a more proactive approach: searching for physical objects associated with extraterrestrial technologies. Professor Avi Loeb is the Frank B. Baird Jr. Professor of Science and former Chair of the Department of Astronomy. THURJ Original Content Writer Andrés Muedano recently had the opportunity to meet with him to discuss his work and motivations.

Andrés Muedano (AM): Thank you for the opportunity to speak with you! Could you please tell me more about yourself and your research?

Avi Loeb (AL): I grew up on a farm in Israel, and I was mostly interested in philosophy at a young age—in the most fundamental questions about our existence. However, in Israel, it’s obligatory to serve in the military at age 18. There was an option for me to be in a program that allowed me to pursue physics and mathematics, and that was the closest I could get to philosophy.

I finished my Ph.D. at age 24 in Physics and Mathematics, and then I was offered a position at the Institute for Advanced Study at Princeton University. I was then offered a position at Harvard and was tenured three years later, so I’ve been here for 30 years—not that I’m counting!

Between 2011 and 2020, I was the chair of the Astronomy Department. I also was the founding director of the Harvard Black Hole Initiative. In recent years—over the past 5 five years or so—I have focused on the

search for life in the cosmos. I wrote a textbook called Life in the Cosmos, published in 2021, and also established the Galileo Project, which aims to search for technological objects near Earth that were manufactured by another [non-terrestrial] civilization.

AM: Tell me more about the Galileo Project. How does it differ from past efforts seeking to find extraterrestrial life?

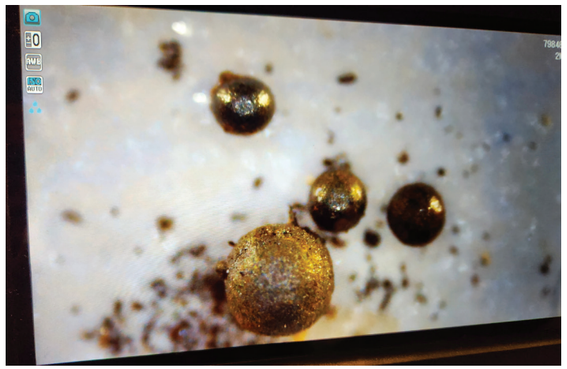
AL: In the past, the search for other [intelligent extraterrestrial civilizations] focused on looking for either radio or laser signals. However, that is like waiting for a phone call at home: [it's possible that] znobody may call you while you're waiting. However, there is a completely different method. You can be active and go out and check your mailbox to see if there are any packages. The sender may be dead, but he doesn't need to do anything. If he sent any packages, the packages will still be waiting for you.

So far, we have sent five probes to interstellar space over the past 50 years: Voyager 1, Voyager 2, Pioneer 10, Pioneer 11, and New Horizons. Now, many stars are billions of years older than the Sun, and we know that it takes less than a billion years to move from one side of the Milky Way galaxy to the other with a Voyager-like spacecraft. So that means that they could have reached us by now!

"Such probes would be bound by gravity to the Milky Way. They would not escape, so they would keep accumulating over time—just like plastics in the ocean."

Nobody had searched for such objects, and only over the past decade have we found the first three of them; two of the three were unlike the rocks that we are familiar with in the solar system. That was intriguing to me.

I therefore established the Galileo Project to do a systematic search for interstellar objects. Just recently, we established that a meteor that landed near Papua New Guinea in 2014 is interstellar—that is, originating from outside our solar system. This meteor was moving faster than 95% of the stars in the vicinity of the Sun, relative to the mean motion of objects in the Milky Way. It was moving very fast at 60 kilometers per second, and it also was able to maintain its integrity up to a very high stress in the atmosphere when it collided with Earth. That implied that it is tougher than all of the space rocks that NASA has cataloged over the past decade—272 of them. It intrigued me: it could have been a Voyager-like meteor. Imagine our own spacecraft colliding with a planet like the Earth; it would appear as a meteor of unusual material strength and high speed. Just this summer, I led an expedition to retrieve the materials from [this object], and we found molten droplets along the meteor path that were never seen before. These droplets are made of a composition that cannot be found on Earth, the Moon, Mars, or asteroids; we are still finishing the analysis, but it is all very exciting because it's the first time that scientists put their hands on materials from a big object that came from outside the Solar System.



Spherules showing up on the microscope image of magnetic particles collected along the most likely path of IM1. Photo courtesy of Avi Loeb.

AM: Besides leading the Galileo Project, you are also a member of the Origins of Life Initiative, a community of Harvard scientists seeking to determine if life is abundant in the universe. How do you see the Galileo Project and the Origins of Life Initiative as complementary to each other?

AL: The search for life involves both primitive forms of life—microbial life and intelligent life. The fundamental question is which one is easier to detect. You might think that microbial life is much more prevalent and therefore easier to find, but that's not necessarily the case, since the imprint of primitive life is subtle. You need to look indirectly for molecules in the atmospheres of exoplanets that might be indicative of life, such as water, oxygen, and methane. The problem with that approach, however, is that even when you find these molecules, there is still the fundamental question of whether they were produced by some other natural process and not by life itself. On the other hand, looking for the technological imprints of a civilization might be relatively straightforward. For example, if there is a large amount of space trash due to other civilizations over the past few billion years, then you know that there was some technological process that produced it. That might be easier to find, especially if there is a large abundance of these things.

"We don't know what we might find in either one of these pursuits, but I would argue that it may actually be easier to find intelligent life."

So far we haven't [found anything], but it may well be that the Galileo Project will find objects that imply a technological origin, and that would be the first time that we ever find such a thing.

AM: The search for extraterrestrial life has been met with controversy, thereby discouraging scientists from working on this topic. Ultimately, this constitutes a problem in the search for extraterrestrial intelligence: the controversy surrounding the idea hinders us from further exploring it. What do you make out of this?

AL: When you say extraordinary claims require extraordinary evidence, but you're not looking for the evidence, then you will never find that you're wrong.

"And I say, let's be agnostic. Many times in science, you don't know whether you will find something that you're looking for."

Think of other areas of research in physics. There was $10 billion invested in the Large Hadron Collider at CERN to look for the lightest supersymmetric particles. Supersymmetry was believed by the majority of the particle physics community, and we haven't found any trace of supersymmetry. On the other hand, we do know that we exist. We know that, over the past 50 years, we sent five probes to interstellar space. We know that there are tens of billions of stars like the sun. We know that a substantial fraction of them, somewhere between a few percent to a few tens of percent, have a planet the size of the Earth, roughly at the same separation from these stars. So I say, it's common sense to suggest that we search for something like us!

AM: Why do you think people are hesitant to accept such a suggestion?

AL: We like to think that we are extraordinary, and it's arrogant for us to think that. People only think that because it boosts our ego, and we have been wrong about that in the past: we thought that we were the center of the universe. For a thousand years, after Aristotle, people preferred to believe this because it gave them a good feeling. Then came Galileo, who was willing to look through the telescope, and he saw the moons of Jupiter revolving around Jupiter, not around us. The clergy refused to look through his telescope, and he was put under house arrest. But the Earth kept moving around the Sun. So it's not a popularity contest—it's not a question of how many likes you get on social media for an idea. In the end, the definition of controversial has nothing to do with whether an idea is a good one. It has to do with how ignorant or motivated people are to argue one way or another.

The fact that it's not common sense for scientists to engage in the search for intelligent civilizations, to me, is a shortcoming of academia. It should be part of the mainstream! There are lots of people who ridicule this effort and argue against it. Interestingly, the search for molecules in the atmosphere of planets—which might not be indicative of life—is part of the mainstream now, because it doesn't threaten our ego: we can still think of ourselves as superior relative to microbes, and we can still believe that we are unique and special and important. But it is quite arrogant to do that, as we are probably

not the pinnacle of creation.

We just need to search for 30 years and invest billions of dollars in the search for objects that might have a technological origin, and if we don't find anything, we will be exactly at the same point as the search for dark matter particles. The public cares so much about this—about 55 percent of Americans believe in intelligent extraterrestrial life. That's more than the fraction of Americans that believe in a biblical god. So given that the public pays taxes to fund science, it sounds completely natural for us to engage in [the search for extraterrestrial intelligence].

So, to summarize, the origin of life on Earth ultimately led to intelligent life. The question is whether that also happened in exoplanets. One way to look for intelligent life is to search for distant electromagnetic signals, but you need to intercept them at the right place and time, and they may be very far away right now. The advantage of looking for objects that were launched into interstellar space is that they would be around because they are bound by gravity to the Milky Way, and that's what the Galileo Project is doing. In the end, that is also part of the Origins of Life research: if we find intelligent life, we know that there is also non-intelligent life that led to it.

"In the end, it's sort of like a race. The question is what we will find first."

This interview was edited for clarity.

Abraham "Avi" Loeb. Photo by Santiago A. Saldivar.

The Sins of Memory in the Digital Age

An Interview with Professor Daniel Schacter

Professor of Psychology, Daniel Schacter Phd. featured above. Photo from the Harvard Brain Science Initiative.

Theo Tobel '27

Dr. Daniel L. Schacter is the William R. Kenan, Jr. Professor of Psychology at Harvard University and former Chair of the Psychology Department. In his more than 30 years of teaching and research at Harvard, Professor Schacter has studied the nature, function, and errors of memory from a cognitive and neuropsychological perspective. As the principal investigator of the Schacter Memory Lab, he is currently working on understanding how memory impacts imagination, creativity, and planning. Professor Schacter's 2001 book The Seven Sins of Memory: How the Mind Forgets and Remembers is a culmination of his life's work. The book's 20-year update (published in 2021) explores how groundbreaking research in cognitive neuroscience has impacted the way we view the idiosyncrasies of memory.

Theo Tobel (TT): Professor Schacter, thank you for taking the time to speak with me today. In your book The Seven Sins of Memory, you determined that errors in memory often reflect the operation of adaptive processes in human evolution. Could you please explain and expand on this idea?

Daniel Schacter (DS): When I first started writing about the seven sins—transience, absent-mindedness, blocking, misattribution, suggestibility, bias, and persistence—and was attempting to organize memory errors, I realized that memory errors can have huge consequences in everyday life. For example, mistaken eyewitness identification, which is due to the sin of "misattribution," is a major cause of wrongful convictions. So then I wondered, why do we still have such an error-prone memory system? There must be some evolutionary advantage to these memory errors.
The sin of misattribution—when you correctly remem-

ber aspects of an event or experience but misremember the source of the event—illustrates these evolutionary advantages. As in the case of wrongful convictions, a witness may claim that they saw a certain individual committing a crime, when in fact this is a mistaken testimony: the person they recognize was at the crime scene but was not committing the crime. This memory error helps us in most cases because it allows us to remember the gist of the event. Most of the time, the source of the event is not all that important—instead, we internalize the general sense of what happened in the situation.

"There must be some evolutionary advantage to these memory errors."

The usefulness of memory's sins can be further exemplified by the very first sin of memory, "transience," which is a gradual loss of information over time. How does this sin assist us? If we recorded everything that happened and constantly had access to it, that would be potentially impossible to manage—we'd be overwhelmed with trivial details. So transience allows us to selectively retain only the most evolutionarily-important information. This same logic can be applied to the six other sins, and thus I arrived at the conclusion that these sins may in fact be beneficial.

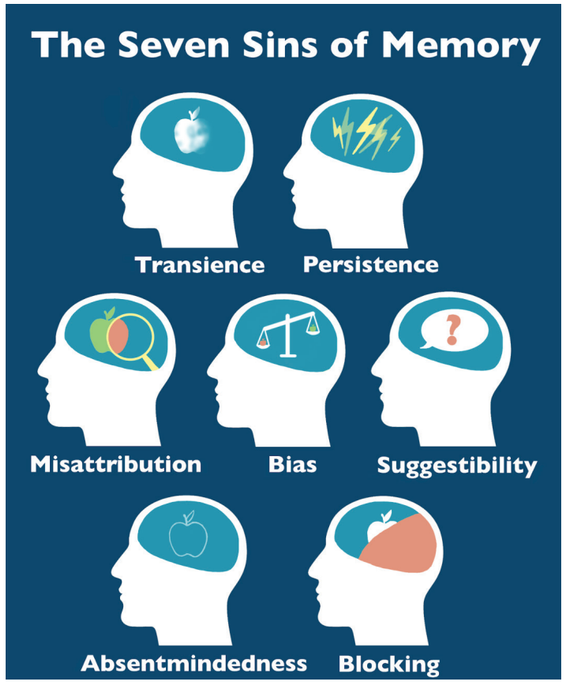
TT: In the process of selectively encoding and reconstructing memories, are memories with positive and negative valence retained differently?

DS: Generally, we know that emotionally-arousing experiences—either positive or negative—are retained over time more so than neutral experiences. There's some evidence that supports the hypothesis that negative events can be retained more specifically and with a greater recall of particular details.

TT: If the negatively charged memories are more specific, would you say the brain has adapted to avoid pain rather than seek pleasure?

DS: I'm not sure if I'd go that far, but this definitely relates to the seven sins and specifically the seventh sin, which I call "persistence." This is the idea that experiences—especially traumatic ones—can persist in the mind in vivid detail. They may become so intrusive that they interfere with psychological functioning, which can result in depression and other debilitating conditions. We must ask again, why is that so? I go back to the adaptive perspective, which holds that remembering negative experiences may allow us to avoid something in the future that could threaten our survival, and yet we have a negative side effect that I call persistence.

TT: The concept of false memories and the formation of memories that are completely fabricated is particularly



Graphic by Xinyi Christine Zhang '27

intriguing to me. How can people distinguish between "deep fakes" and real sources so that they can avoid the formation of these false memories?

DS: There have been many brain imaging studies on this, and most find that true memories activate areas of the visual and auditory cortices more than false memories, but that's not always the case. People also tend to believe fake news that aligns with their pre-existing beliefs—this is a type of confirmation bias, so it's important to be aware of the role bias plays in the formation of these memories. I also think that deep fakes are so

widely publicized that everyone is aware of this possibility when reading the news. Therefore, we must be careful critics of our sources and use our judgment to determine the validity of information online.

"People also tend to believe fake news that aligns with their pre-existing beliefs—this is a type of confirmation bias, so it's important to be aware of the role bias plays in the formation of these memories."

TT: Is it possible to "expel" false information from your memory and rid yourself of those biases?

DS: It's difficult. In the 1990s, Elizabeth Loftus showed this with the "lost in a shopping mall" study. Loftus found that it was possible to implant memories of events that never occurred—that participants had been lost in a shopping mall as a child—merely through suggestion. When most participants were first asked to remember this event, they said, "No, that never happened to me." However, when participants were repeatedly questioned, more than a quarter of them "remembered" the false event. Even more so, after these participants were debriefed and told that the event in question never occurred, some remained steadfast in their beliefs that this fabricated memory was real (Loftus & Pickrell, 1995).

TT: I think this is especially relevant now, as we have seen increasing rates of fake news and misinformation appearing in news coverage and in our everyday lives. Since your 20-year update of The Seven Sins in 2021, there have been drastic technological advancements, such as the public release of large language models like ChatGPT. Do you think that these advancements will have an impact on memory errors? If so, how?

DS: It's hard to say—ChatGPT hasn't even been publicly available for a year, yet it is so prevalent in every field. One of my graduate students, Will Orwig, is studying the relationship between memory and creativity, which I have been fascinated with for many years. This connection is based on the principle that our episodic memories (memories of personal experiences) allow us to generate creative ideas because memories themselves are reconstructions of the past. ChatGPT does the same thing: it is an intelligent program that uses diverse and detailed ideas to create new, nuanced ideas. We must ask ourselves if our ideas are more creative than this model's, and in Will's study of creative writing, we find that ChatGPT writes stories that are just as creative as those written by human participants. I can't say for certain how these advancements will impact memory errors because there haven't been enough studies on this question yet.

TT: How have scientific advancements affected your work and your research?

DS: The emergence of neuroimaging technologies such as PET scans and fMRI transformed memory research—these tools allowed researchers such as myself to observe brain activity and the specific brain regions that "light up" during certain cognitive processes and memory tasks. At the time, it was almost like something out of your favorite science fiction novel—just unimaginable a decade earlier.
Scientific advancements have also affected and possibly impaired humans' memories. There is a ubiquitous concern that technological innovations, such as GPS, may have a negative impact on a person's overall spatial memory, not just their ability to remember the route to the dentist's office that the navigation system is now providing them.

"There is still a pretty substantial gap between the "systems" level of neuroscience—which encompasses the study of memory—and the cellular or molecular levels."

Psychological experiments indicate that a device such as GPS can impair memory of specific routes, something we'd call a task-specific effect. On the bright side, there's very little evidence that GPS has a general impact on memory impairment—it is difficult to ascertain correlation from causation (i.e. people who use GPS are more likely to have a worse memory in the first place).

TT: Where do you think there are still gaps in our understanding of memory, and what types of research can be done to address these gaps in knowledge, either for memory or in psychology in general?

DS: Wow, that's a big question. There is still a pretty substantial gap between the "systems" level of neuroscience—which encompasses the study of memory—and the cellular or molecular levels (i.e. looking at neurons and genes). Very recently, there's been exciting progress in mapping neural connectivity and generating ultra-sharp scans of the entire mouse brain (Johnson et al., 2023). In general, though, there's still a lot of research and innovation to be done to narrow that gap.

TT: As a renowned memory researcher, do you have any recommendations for students looking to avoid succumbing to the sin of transience? Is there a special trick for remembering material for midterms or final exams?

DS: Well, there are a number of them, and they're pretty well documented, but I think probably the best one is retrieval practice or self-testing. In my update of The Seven Sins, I wrote about the testing effect, which shows that active recall not only helps you strengthen your knowledge of the material but specifically helps with retaining information over time. The effort to retrieve information through quizzing yourself and making concept maps and flashcards instead of reading the material over and over again is sure to boost your memory.

TT: I have a math midterm next week, so I'll be sure to use that technique. That's all the questions I have—I'm really so thankful and so honored to speak to you about memory and its implications and unknowns. Thank you so much for your time.

This interview has been edited for clarity.

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Climate Change, Pandemics, and the Quest for Environmental and Social Justice

Image of Landfill. Photo from iStock.com/vchal

Saketh Sundar '27

Introduction

Heat waves, wildfires, and unprecedented hurricanes. Never more than in the past year has our world grappled with the unprecedented challenges induced by the modern climate crisis. The extensive consequences of a progressively warming planet have not only affected our economies and ecosystems but have also profoundly impacted individual and global health. Climate change, as an increasingly imminent threat, has triggered a series of interconnected health concerns that are becoming ever more challenging to address as the crisis continues. T ese issues of global health require expedient action to minimize the risks of disease, disability, and death caused by our changing world.

Direct Effects of Climate Change on Health

Climate change manifests its influence on health through various direct pathways, with one significant aspect being the escalation of extreme weather events, including heatwaves, storms, and flooding, all of which are directly linked to the shifting climate. These weather extremes have both immediate and long-term health implications (Ebi et al., 2021). For instance, heatwaves can lead to heat-related illnesses and fatalities, particularly among vulnerable populations such as the elderly and individuals with preexisting health conditions (Arsad et al., 2022). Such extreme weather events often force the mass migration of populations, which exposes people to risks of disease, malnutrition, or violence. Moreover, extreme weather events like wildfires and hurricanes release high amounts of pollutants, displacing communities and inducing pollution-associated health problems (Ebi et al., 2021). There is also an im-

mense psychological toll of extreme weather events on affected communities, often characterized by anxiety, post-traumatic stress, and depression, which highlights the broader impact on community mental health (Makwana, 2019).

Additionally, climate change impacts air quality through multiple means, significantly affecting individual and public health. Increased concentrations of atmospheric greenhouse gasses raise global temperatures, worsening air pollution by creating ground-level ozone and particulate matter, which harm respiratory and cardiovascular health (Rice et al., 2014). Prolonged exposure to poor air quality has been linked to asthma, bronchitis, heart disease, and premature death (Jiang et al., 2016).

In addition to these direct effects, climate change plays a significant role in the spread of infectious diseases. Global warming significantly impacts the dissemination and intensity of various diseases by modifying the geographical distribution, behavior, and temporal patterns of living disease vectors, including mosquitoes, ticks, and agricultural animals (Campbell-Lendrum et al., 2015). The escalation in global temperatures has broadened the habitat range of these vectors, consequently facilitating the transmission of diseases such as malaria, dengue fever, and Lyme disease across international borders and into regions where they were previously infrequently encountered. Furthermore, the prolonged warm seasons induced by climate change foster more conducive circumstances for disease transmission by increasing the range of time in which vectors can thrive, thereby amplifying the prevalence and spread of outbreaks (Caminade et al., 2019).

Furthermore, environmental factors have been instrumental in shaping the dynamics and outcomes of pandemics. A pertinent example can be found in the Zika virus pandemic of 2015–2016, where changing environmental variables—particularly those associated with temperature and vector behavior—were instrumental. Climatic alterations marked by rising temperatures not only extended the geographic range of the Aedes mosquito—a crucial transmitter of the Zika virus—but also facilitated the virus' transmission, consequently enabling its penetration into previously unaffected regions (Ryan et al., 2019). Furthermore, the Ebola virus outbreaks in Africa have exhibited a similar reliance on environmental circumstances. Deforestation and habitat degradation in the African tropics have engendered shifts in ecological dynamics, precipitating heightened human-wildlife interfaces Alexander et al., 2015).

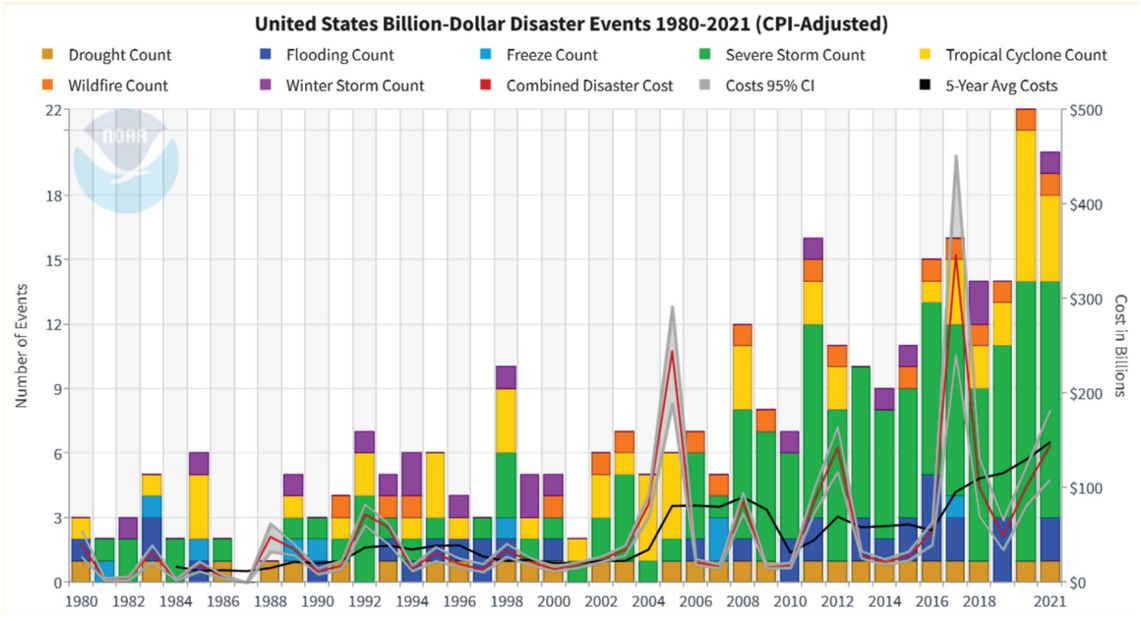


Fig. 1: Rising number and cost of disaster events from 1980-2021 (NOAA)

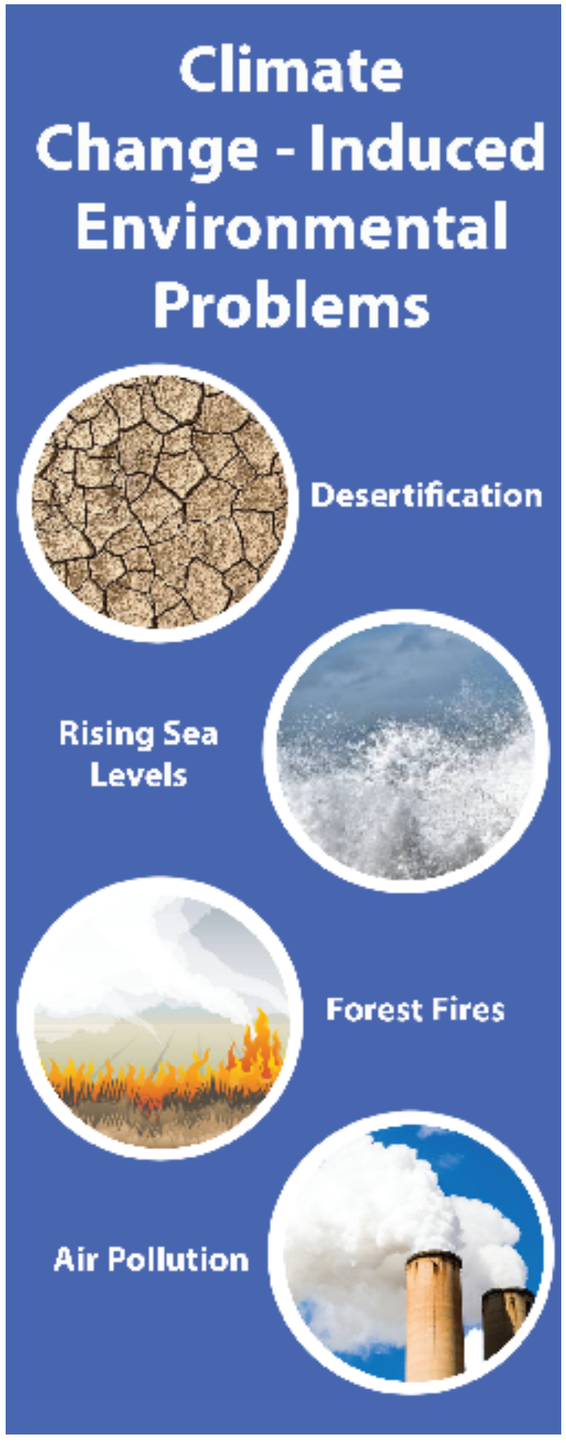
These altered interactions have subsequently raised the risk of zoonotic spillover events, leading to outbreaks of the Ebola virus among human populations.

Understanding the various impacts of climate change on global health is facilitated by the concept of "One Health." This holistic and interdisciplinary strategy, championed by institutions like The Centers for Disease Control and Prevention (CDC), recognizes the interconnectedness of human, animal, and environmental health. By emphasizing the interdependence of these domains, the concept of One Health underscores the need for collaborative efforts across disciplines to address complex global health challenges, such as zoonotic disease transmission and environmental degradation, to attain optimal health outcomes for all (Mackenzie & Jeggo, 2019).

The Unequal Burden of Climate Change on Global Health

The harmful impacts of climate change, while increasing for all people, are significantly amplified for those people in marginalized communities. This amplification can be attributed to the existence of long-term socioeconomic disparities and discriminatory land-use practices that impede the access of these communities and the people residing in them to essential resources (Poverty, Livelihoods and Sustainable Development, n.d.). Consequently, they become more susceptible to the devastating consequences of natural disasters and other climate change-related health issues. For example, these communities sometimes inhabit inadequately constructed dwellings situated in regions prone to flooding, thereby exacerbating the hazards and repercussions of extreme weather events.

These communities also frequently encounter restricted access to healthcare services as a result of socioeconomic or geographic factors, including distance from healthcare providers and financial limitations that hinder their ability to afford healthcare. During climate-related emergencies, such as heat waves or hurricanes, these communities confront even more significant obstacles in obtaining medical assistance, resulting in delayed treatment and deteriorating health (Climate Change and Health Equity, 2023). In everyday life, marginalized communities are already vulnerable to poor health outcomes and may experience extra difficulties



Graphic by Sabiha Amin '27

in accessing nutritious food and clean water sources. Some marginalized communities live in "food deserts," where they have limited access to fresh, healthy foods and affordable options are high-processed and less nutritious than others (Karpyn et al., 2019). Consequently, diet-associated diseases—including cardiovascular disease and type 2 diabetes—can become more prevalent in such communities, rendering them prone to the harmful impacts of public health crises such as pandemics (Seligman et al., 2010). The challenges associated with accessing fresh, healthy foods are further exacerbated by climate change increasing the costs of food production.

The COVID-19 pandemic serves as a clear illustrator of the presence of disparities in healthcare access on a global level. Developed nations managed to obtain and distribute vaccines at a significantly higher pace in comparison to developing countries, resulting in limited availability of life-saving vaccines for vulnerable populations in low-income communities and nations (Md Khairi et al., 2022). This unequal distribution of vaccines highlights the manner in which catastrophic public health crises are amplified by the existing inequities in healthcare access across different countries.

Furthermore, climate change-induced environmental problems, such as rising sea levels and extreme weather, have given rise to the global phenomenon of climate refugees. Directly, these challenges have led people and communities to desert their homes out of fear of the effects of changing environments, such as access to food, shelter, or water. The challenges faced by climate refugees include relocation, lack of means of earning their living, limited legal protection, overcrowding of the reception areas, and lack of the required infrastructure.

By comparison, the water crisis in Flint, Michigan, exemplifies a domestic situation of environmental injustice. The choice to switch the city's water source to the Flint River resulted in the contamination of the water supply with lead, which had a disproportionate impact on African-American communities with the city being predominantly African-American and a significant portion of the population under the poverty line (Campbell et al., 2016). This situation highlights the fact that marginalized communities frequently experience the negative consequences of environmental policies, which in turn lead to detrimental health outcomes.

Environmental Justice & Global Health

The relationships between social injustice, healthcare disparities, and public health crises are intricately woven. Social injustices, which encompass disparities in healthcare access, economic inequality, and systemic discrimination, significantly amplify the repercussions of public health crises. These disparities entail unequal access to healthcare resources and heightened disease burdens, thereby fostering increased disease transmission during public health crises. Moreover, economic disparities—closely intertwined with social injustice—confer vulnerability upon marginalized communities through compromised living conditions, reduced educational opportunities, and inequities in healthcare access and quality. Discrimination and bias within healthcare settings further exacerbate these disparities, resulting in disparate health outcomes. The workforce in low-paying but essential roles, often lacking adequate benefits, faces increased risks of disease transmission, while crowded living conditions impede effective public health precautions (Shadmi et al., 2020). Additionally, disparities in health education hinder the capacity of some to follow public health guidelines. An example is vaccine hesitancy, stemming from historical injustices and discrimination, which further complicates pandemic responses (Njoku et al., 2021).

Systemic racism exerts a profound influence on health outcomes, giving rise to enduring disparities in healthcare access, quality, and overall well-being among racial and ethnic minority populations. This phenomenon underscores the historical and institutional inequities that continue to perpetuate health disparities, with minorities often facing challenges in accessing healthcare due to factors such as geographical disparities, transportation limitations, and inadequate insurance coverage (Gee & Ford, 2011). Additionally, systemic racism fosters disparities in the quality of healthcare delivered to these populations, manifesting in areas such as pain management, chronic disease management, and maternal health. This issue is further compounded by discrimination and bias within healthcare settings. The adverse impacts of systemic racism also extend to mental health—with minority populations experiencing higher rates of mental health conditions (Williams, 2018)—and to maternal health, notably affecting Black women with elevated rates of maternal mortality and adverse birth outcomes (Njoku et al., 2023).

Equitable access to healthcare, as previously discussed in the context of addressing systemic racism, is of paramount importance. Systemic racism can exacerbate healthcare disparities, making it even more crucial to address these disparities through equitable access. When individuals from marginalized racial and ethnic groups face unequal access to healthcare, it perpetuates the cycle of systemic racism and contributes to poorer health outcomes for these populations. Ensuring equitable access to healthcare, regardless of one's background, is a key strategy for dismantling systemic racism in healthcare and promoting health equity. This approach aligns with the principles of fairness and social justice and contributes to improved public health outcomes.

Efforts to Ameliorate Global Health and Environmental Injustice

Environmental and social activism plays an indispensable role in addressing the pressing issues of climate change and social justice. Activists and grassroots organizations are instrumental in advocating for change at both the local and global levels. Their efforts encompass raising awareness, mobilizing communities, and pressuring policymakers and corporations to adopt more sustainable and equitable practices. These activists often serve as catalysts for initiating critical conversations around climate action and social justice, compelling stakeholders to acknowledge the urgent need for change. Their advocacy not only provides a vital counterbalance to vested political and economic interests but also fosters an environment where issues like environmental sustainability and justice are given the attention and priority they deserve. For example, in the United States in 2017, several indigenous activists protested the construction of the Dakota Access Pipeline, which threatened to pollute the Standing Rock Sioux tribe's water source and sacred lands (What to Know about the Dakota Access Pipeline Protests, 2016). Their peaceful protests drew global attention, leading to delays and legal challenges. Although the pipeline was eventually completed, the activism spotlighted issues of environmental justice. The Natural Resources Defense Council (NRDC), another entity, has held a prominent position as the primary authority on the Clean Air Act over the last few decades. During this time, they have leveraged the Act in legal proceedings against significant polluters, particularly those that have had a disproportionate impact on low-income communities (Racial Disparities and Climate Change, 2020).

On a larger scale, global cooperation and policy changes are paramount in addressing the interconnected challenges of climate change and social justice. Climate change, for instance, is a global crisis that requires collaborative efforts to mitigate its impacts. International agreements such as the Paris Agreement exemplify the importance of global cooperation in tackling climate change, as they provide a framework for nations to collectively work toward common goals (Skjærseth et al., 2021). Similarly, addressing social justice issues, including economic inequality and racial discrimination, necessitates international collaboration and the reformation of policies and systems that perpetuate such disparities. National policies that promote equity, inclusivity, and environmental sustainability are crucial in effecting change on a global scale. Potential solutions include implementing carbon footprint pricing mechanisms, supporting renewable energy transitions, and advancing social justice policies, such as affirmative action and inclusive economic development strategies. Ultimately, the success of these efforts hinges on the cooperation of nations and the alignment of their policies with the goals of a more just and sustainable world.

Addressing climate change, public health crises, and social injustice requires a nuanced, multifaceted approach. Solutions for climate change involve transitioning to renewable energy sources, implementing sustainable practices in industries, and promoting sustainable land use and resource management. To combat public health crises, we need robust public health infrastructure, global surveillance systems, and equitable access to vaccines and healthcare. For social injustice, inclusive policies that focus on economic and educational opportunities for marginalized communities should be enacted, while education should emphasize empathy, understanding, and advocacy for social and environmental justice.

Inclusive policies and education are vital components of effecting meaningful change. Moreover, they are essential for reducing disparities and ensuring that the benefits of sustainable practices and healthcare access are equitably distributed. Education plays a critical role in raising awareness, fostering empathy, and nurturing informed citizens who can actively engage with envi-

ronmental and social justice issues. Furthermore, education can empower individuals to become advocates for change, helping to drive collective efforts toward a more equitable and sustainable future. Advocating for a just transition to a more sustainable future is imperative. This transition involves creating pathways for marginalized communities to benefit from green jobs and sustainable practices, ensuring that the transition is not only environmentally responsible but also equitable. It is crucial to support policies that prioritize social and environmental justice, recognizing that true sustainability must prioritize both the planet and its inhabitants. By actively championing these principles and encouraging systemic change, we can contribute to a more just, resilient, and sustainable world for all.

Conclusion

The interconnectedness of climate change, public health crises, and social/environmental justice highlights that these challenges cannot be effectively addressed in isolation. Climate change exacerbates public health crises and disproportionately impacts vulnerable communities, while social injustice intensifies these crises. The urgency of action is evident, as the consequences of inaction are dire, affecting not only the well-being of individuals but the stability of societies and ecosystems. It is imperative that individuals, communities, and countries act swiftly and decisively to combat climate change, address public health crises, and promote social and environmental justice together. By supporting sustainable and equitable initiatives, advocating for inclusive policies, and championing education, we can collectively contribute to a more just and sustainable future. Each of us can play a part in this transformative journey, ensuring that future generations inherit a world that values both the planet and its people

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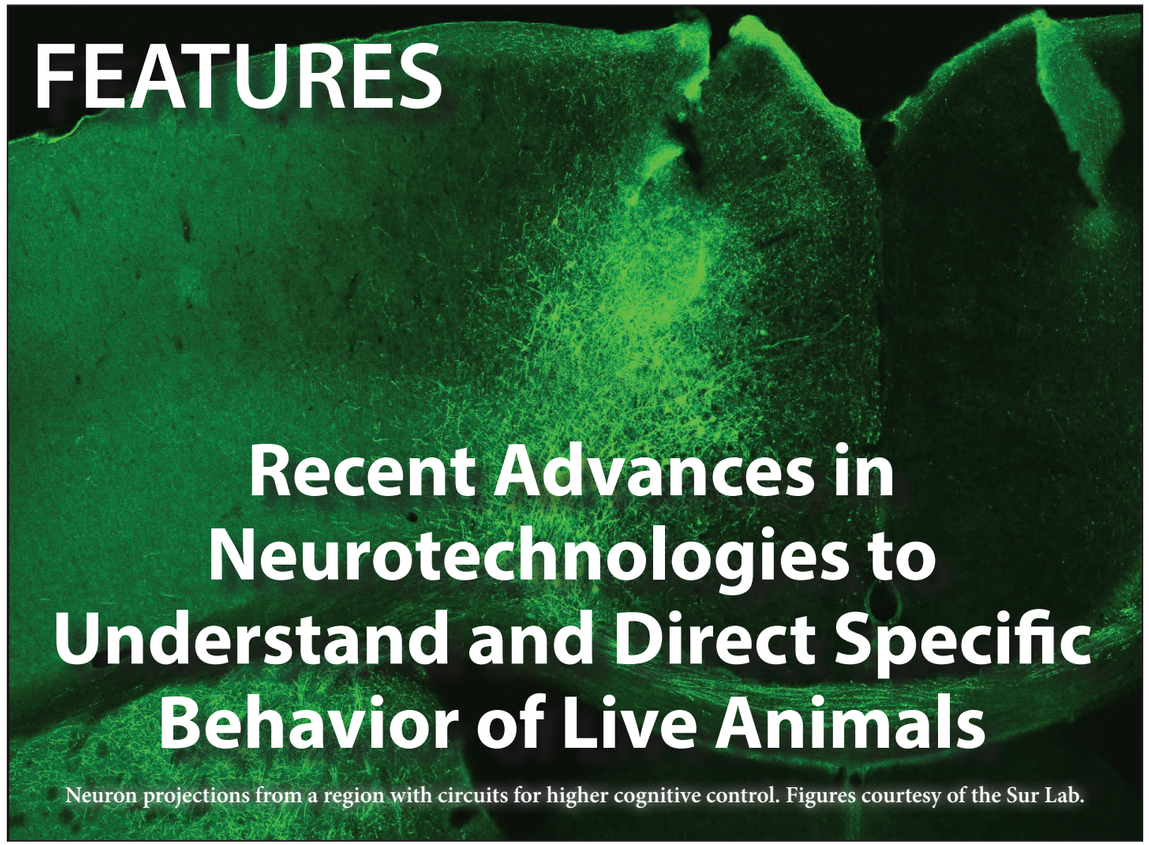

Recent Advances in Neurotechnologies to Understand and Direct Specific Behavior of Live Animals

Neuron projections from a region with circuits for higher cognitive control. Figures courtesy of the Sur Lab.

Paula Zhu '24
(*figures by Alyssa Suh '25*)

Introduction

Neuroscience has traditionally faced difficulty in accessing and understanding the behavior of the brain at a single-cell level. Many of these challenges are due to the brain's complexity; the brain has 100 billion neurons and well over 100 trillion connections and synapses, all operating at a millisecond timescale with functionally distinct circuits crossing over each other within microscale regions. However, starting with breakthroughs in the 2000s, such as fluorescent genetically-encoded calcium ion (Ca2+) indicators (GECIs)—where Ca2+ detection is used as a proxy of neural activity—and optogenetics—where neuron firing is controlled using light-sensitive ion channels in neurons—new advances in revolutionary neurotechnology have made it increasingly feasible for neuroscientists to understand how the brain operates on a cellular level. In the past few years, four distinct categories of neurotechnology advances have catalyzed this change in understanding, including chemogenic control, electrical recording and control, optogenetics-based control, and optogenetics recording and visualization.

1) Chemogenetic Control

Chemogenetic control is the use of chemical and genetic engineering to control cellular processes. Traditional pharmacology typically manipulates the uptake and degradation of natural neurotransmitters, acts as a direct agonist/antagonist (stimulant/blocker) of naturally occurring receptors or affects natural cell signaling pathways. However, these pharmacological methods lack any specificity beyond the distribution of the endogenous drug target. One major attempt at chemogenetic control sought to address these challenges associated with the lack of pharmacological specificity.

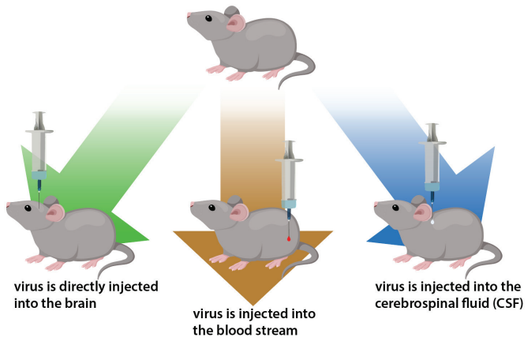

Fig. 1. How to Get Custom Proteins to the Brain

DREADDs and Designer Receptors with Designer Drugs

Chemogenetic designer receptors, known as DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), are artificially engineered G-protein-coupled receptors designed to initiate intracellular signaling pathways that influence neuronal activity. For example, the hM3Dq receptor leverages the native Gq-protein signaling pathway to induce firing, while the hM4Di receptor employs Gi signaling to silence activity. These receptors only respond to designer compounds made to be typically inert and blood-brain barrier permeable, such as recently developed compound-21 (c21), which can be administered in vivo via intraperitoneal injection for use up to several hours or through drinking water for use over several days. While chemogenetic techniques offer precise spatial modulation (control over which cells express DREADDs) and a minimally invasive method of vuse, they do not provide temporal precision superior to traditional optogenetic methods, since their timescale of neural control is dependent on the slow and gradual absorption, distribution, metabolism, and excretion of the designer drug used (Smith et al., 2021).

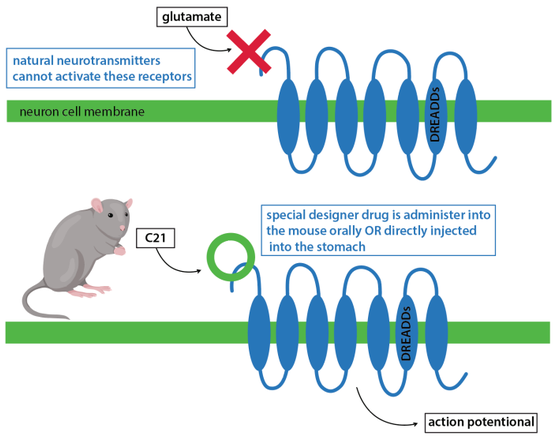

Fig. 2. Designer Receptors Exclusively Activated by Designer Drugs

2) Electrical Recording and Control

In traditional electrophysiology, a sharp electrode is placed near or in neurons to record their activity, which can also lead to tissue damage and an inflammatory response. This invasiveness makes it challenging to study long-term neural activity and limits the number of electrodes that can be implanted in a brain simultaneously. Moreover, electrophysiological recordings are typically limited to a small number of neurons or specific brain regions, making it challenging to understand large-scale network interactions. Ultimately, these limitations restrict traditional electrophysiology to very few recordings at a time, with a high learning curve for quality recordings that do not overly damage the neuron.

Neuropixels and Recording Thousands of Neurons at Once

Many recent neural electrical recording technologies have focused on simultaneously recording a greater spatial coverage and a larger number of neurons. Advancements in lithographic fabrication techniques have allowed semiconductors and electrodes to be scaled down to subcellular dimensions, enabling the recording and stimulation of individual neurons. One common example is the Neuropixels probe, a millimeter-long, micrometer-thick straight silicon shank of high-density electrodes incorporating CMOS circuits for multiplexing and amplification, which maps neuron electrical recordings across multiple functional depths (Jun et al., 2017) (Steinmetz et al., 2021). This year, a recent version of Neuropixels recorded over 3000 single neurons per single probe (Trautmann et al., 2023). Moreover, specific neurons can be selected by combining probe implantation with the expression of optogenetic opsins that induce neuron activation with light – in this way, activity spikes from neurons can be identified as part of, or not part of, a genetically specific population via their response to light. Nevertheless, challenges associated

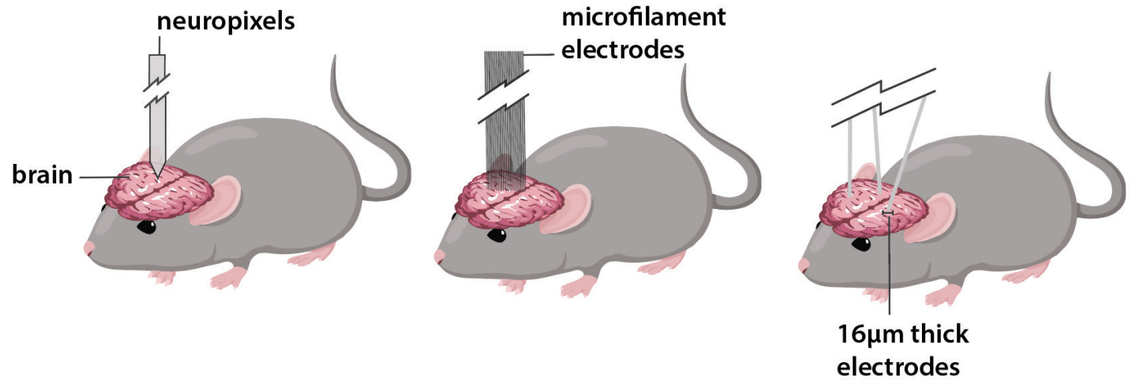

Fig. 3. Different Methods for Neural Electrical Readings

with Neuropixels probes include their relative stiffness, that their insertion can lead to tissue displacement and potential damage, and gradual drift of probe location. This may trigger neuroinflammatory responses affecting the quality of neural recordings over time. Finally, combining Neuropixels with optical techniques may risk confounding the photovoltaic effects of the CMOS devices if experiments are not designed to minimize optoelectric crosstalk and overlap.

Materials for Biocompatible and Long-Term Electrodes

The mechanical mismatch between conventional electrode metals and neural tissue has made it challenging to avoid physical damage and chronic inflammatory responses when using electrodes for neural control. On the other hand, neuro-electronics need low interface impedances (effective output circuit resistance) and physiologically relevant CICs (the charge that can be injected into brain tissue without inducing any irreversible chemical reactions at the electrode surface) to achieve high signal-to-noise ratio and low voltage signal loss measurements. Advances using biocompatible, conductive polymers have been employed to increase both conductivity and material flexibility. For example, a system of 16-micrometer-thick flexible probe modules integrating electrodes of the conductive and biocompatible polymer PEDOT:PSS has shown recordings from up to 1,024 discrete channels in freely moving animals. This technology supported both extended recordings spanning months and tracking of well-isolated neural units across multiple brain regions for over a week (Chung et al., 2019). Likewise, developed in the same year, Neurotassels, an array of up to 1024 flexible, 100-micrometer diameter microelectrode filaments have also been used to record from animals for several months. These filaments spontaneously assemble into

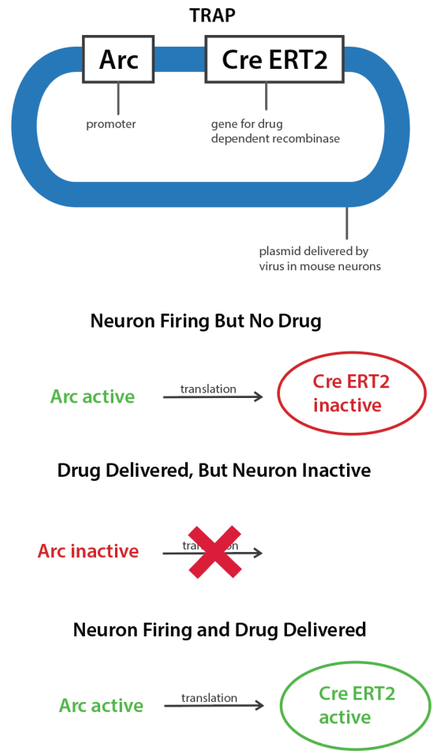

Fig. 4. Targeted Recombination in Active Populations (TRAP) Neurons

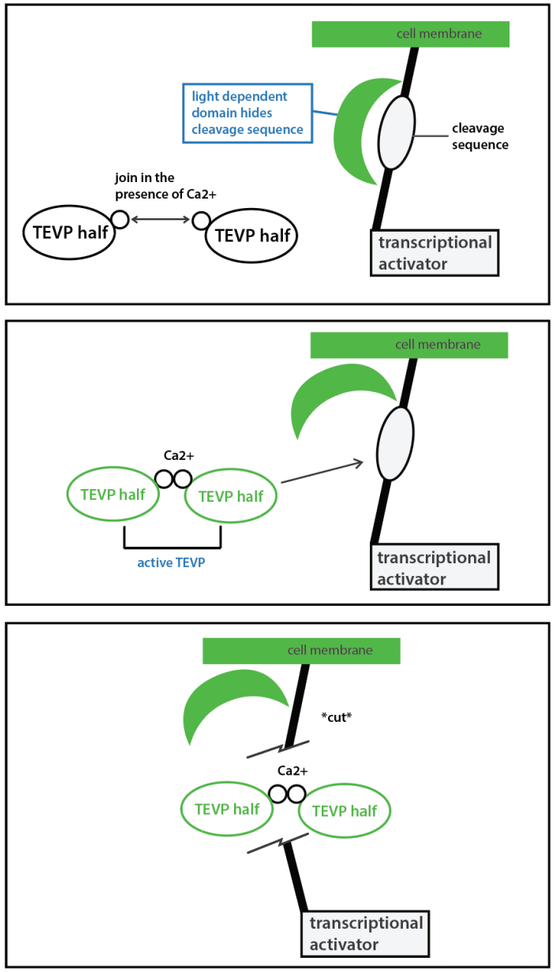

Fig. 5. CalLight cleaving transcriptional activator

implantable fibers upon withdrawal from tissue-dissolvable, molten polyethylene glycol (PEG) polymer (Guan et al., 2019).

3) Optogenetics-Based Control

First developed in a landmark paper in 2005, optogenetic control of cell activity involves the introduction of light-sensitive proteins called opsins in target cells. When exposed to specific wavelengths of light, opsins can activate or inhibit neurons, depending on the type used. The revolution of optogenetics is the establishment of causality between the activity of specific neurons and subsequent animal behavior. Since then, light-controlled systems for manipulating various other aspects of neurons have been developed. Of note, advances in widefield scanning and holographic illumination for large-scale, volumetric access further buttress the advantages of these light-dependent tools.

Targeting Behavior-Specific Neurons

A recombinase, such as Cre or Flp, is an enzyme that will cut a section of DNA based on markers around the gene. They can be used to activate target genes only in cells expressing the recombinase, such as by excising stop codons placed before the target gene. In Targeted Recombination in Active Populations (TRAP), neurons express a drug-dependent recombinase (such as tamoxifen-dependent CreERT2) downstream of a neural-activity-dependent promoter (such as Arc or Fos), leading to increased expression of the recombinase following neural activity (Guenthner et al., 2013). In this way, only when something activates the neuron, such as a behavioral stimulus, and the drug is injected is the recombinase translated and allowed to trigger recombination and activation of target genes. These target genes can include optogenetic proteins or any other tools for neural control. This has famously been used to target neurons to manipulate or create specific memories in live mice (Ramirez et al., 2013). However, the reliance on slow drug kinetics prevents this approach from effectively capturing neurons specific for faster behaviors.

More novel approaches have attempted to condition gene expression to Ca2+ rises triggered by action potentials, such that expression is initiated when both Ca2+ and light are present. For example, CalLight-ST from 2022 uses 1) a split-tobacco etch virus protease (TEVp) connected on either end to domains that bind together with Ca2+ is present and 2) a transcriptional activator tethered by a cleavage sequence hidden by a light-dependent domain to the membrane (Hyun et al., 2022). When Ca2+ is present, TEVp fuses together and becomes active. When light is present, the cleavage sequence becomes accessible. Thus, only when both Ca2+ and light are available is the cleavage sequence cut by TEVp, and the transcriptional activator is released for target gene expression in those specific neurons.

Artificial Neurotransmitter Release and Receptor Binding

Neurotransmitter photo-uncaging enables the precise release of neurotransmitters with both high spatial and temporal control. In this strategy, neurotransmitters are chemically modified by attaching a light-sensitive "cage," rendering it inactive (Ellis-Davies, 2019). When exposed to a focused laser beam, the cage is photo-cleaved and removed, allowing for near-instantaneous release of the neurotransmitter. This has recently been used to mimic natural neurotransmission and cause strengthening or weakening of specific, singular synapses (Noguchi et al., 2019).

Photo-switchable ligands, on the other hand, are tethered to specific target receptors in such a way that their

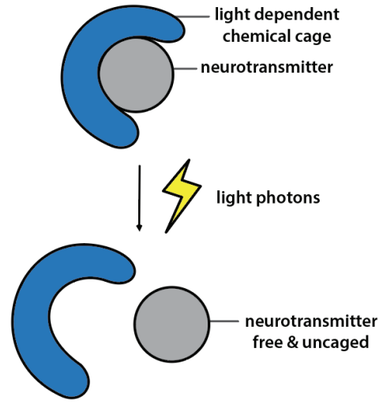

Fig. 6. Light-sensitive chemical cage release

binding is determined by light. Azobenzenes, which switch between cis and trans when exposed to specific light wavelengths, are often incorporated in such a strategy. Upon illumination, the azobenzene-ligand switches configuration and binds the receptor (Kienzler & Isacoff, 2017).

Controlling Specific Intracellular Signaling Pathways and Proteins

Various tools for modulating other cellular pathways using light have also been developed. Recent tools include those for the artificial production of proteins, such as adenylyl cyclase for cAMP (Stierl et al., 2011) or guanylyl cyclase for cGMP (Gao et al., 2015). There are also systems for degradation, such as the auxin-inducible-degron system which activates an expressed plant ubiquitin-ligase complex following exposure to the plant hormone auxin that then degrades all endogenous proteins tagged with degron (Yesbolatova et al., 2020).

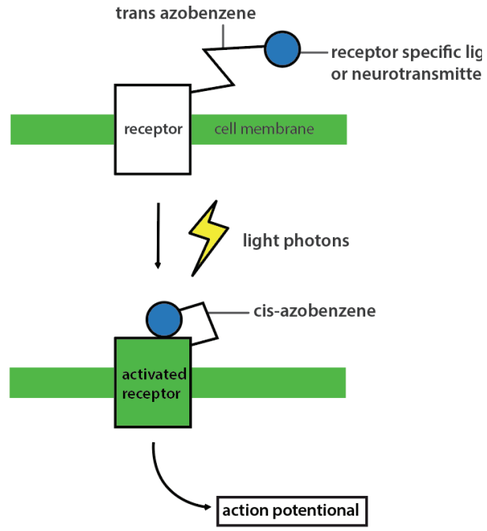

Fig. 7. Photoswitchable Ligands

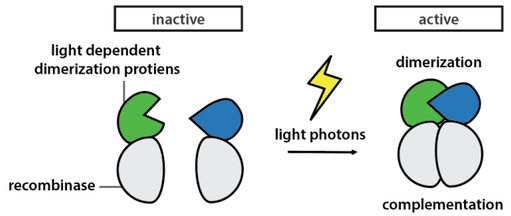

Fig. 8. Light-dependent gene expression

Light-Controlled Transcription and Custom Genetic Patterning

These systems generally involve a genetically engineered system of light-sensitive proteins that allow the expression of a recombinase to specific wavelengths of light. For example, one system developed in 2020 uses a split-Cre recombinase that would dimerize only when given blue light (Morikawa et al., 2020). By directing light to specific neurons, patterning the expression of specific proteins, including optogenetics, can be done with remarkable precision.

Infrared Optogenetics and Remote Control of Neurons

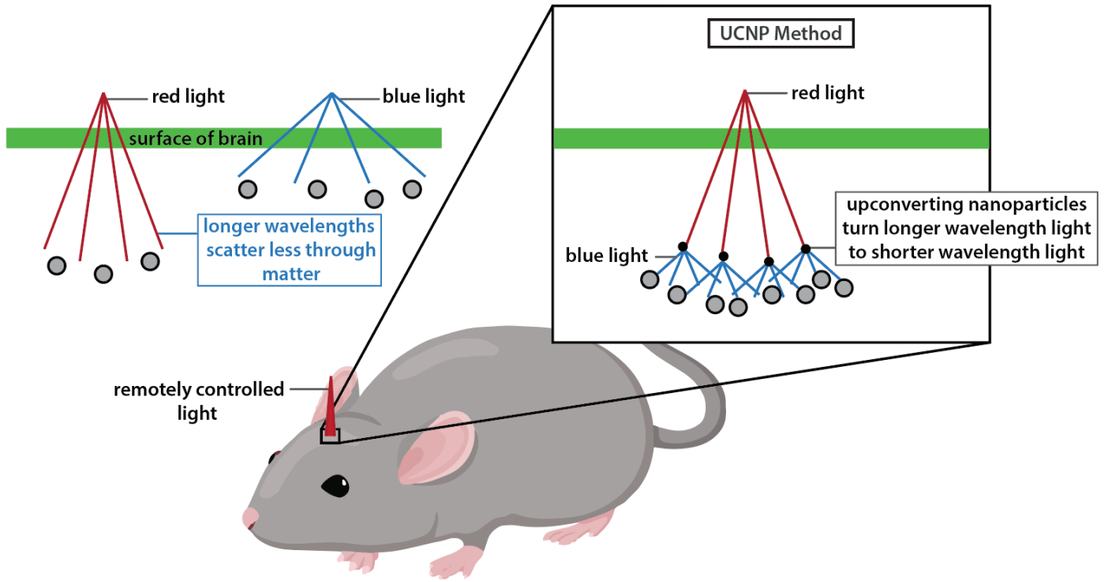

Fig. 9. Infrared Remote Control of Neurons

The penetration depth of visible light is limited by scattering and tissue absorption. As a result, visible light can only czontrol superficial neurons and requires implanting optical fibers for deeper regions. Near-infrared light can overcome these limitations and allow remote control at greater depths within the brain. Combining this with upconverting nanoparticles (UCNPs), which convert infrared to shorter wavelength light, transcranial control of seizure silencing and memory recall was first demonstrated in 2018 (Chen et al., 2018)

4) Optogenetics Recording and Visualization

With the first version developed in 2001, GECIs (Genetically Encoded Calcium Indicators) are a widely used tool in neuroscience for monitoring intraneuronal calcium levels, a proxy for neuronal activity and neurotransmitter vesicle release. Since then, many optical sensors for measuring other facets of neural activity have been developed.

GEVIs and Non-Invasive Optical Visualization of Electrical Potentials

While modern GECIs can report activity from thousands of cells simultaneously at high signal-to-noise ratios, they are still insensitive to precise spike timing and cannot report subthreshold activity. Genetically encoded voltage indicators (GEVIs) report changes in membrane potential with differences in cellular fluorescence, allowing for the optical detection of fast action potentials and subthreshold changes in membrane potential. Because voltage changes in neurons happen rapidly and therefore require high millisecond temporal precision and extremely high signal-to-noise ratios, these tools have historically been inadequate for precise measurements of membrane potential at cellular resolution. Nevertheless, recent progress has resulted in new GEVIs with much-improved sensitivity and temporal resolution. The first modern GEVIs were fusions of voltage-sensitive domains with fluorescent proteins (FPs). These include the currently only known GEVIs to work under 2-photon microscopy, the ASAP family (Evans et al., 2023), based on fusing a phosphatase domain with a circularly permuted green fluorescent protein (GFP) in between.

Alternatively, rhodopsin-based GEVIs, such as the Arch family, are derived from microbial rhodopsins with voltage-dependent near-infrared (NIR) fluorescence. This shift away from the blue light spectrum allows for usage combinations with other blue/green light-dependent tools, including btlue-light activated channelrhodopsin (ChR2) which stimulates action potentials in neurons. Nevertheless, opsin-based GEVIs typically have low fluorescence and quantum yield, meaning they require much higher intensity light for absorption, which combined with the high temporal sampling necessary in voltage recording, can result in significant photobleaching. Photobleaching is when photons, by chance, excite electrons to slightly too stable high energy states, gradually resulting in the formation of extremely reactive species, such as free radicals, that irreversibly damage the fluorescent protein's molecular structure. Thus, FRET (Fluorescence Resonance Energy Transfer)-based variants of opsin GEVIs exist to require less light delivery. FRET is when energy from a higher energy "donor" fluorophore (e.g. a more blue-colored one) excites an electron in a lower energy "acceptor" fluorophore (a more red-colored one), resulting in increased fluorescence of the acceptor over the donor. Examples of FRET-based variants include Ace-mNeon and VARNAM (Kannan et al., 2022) which utilizes FRET between the rhodopsins with other red and green FPs, respectively, and the Voltron family (Abdelfattah et al., 2020) which adds HaloTag, a protein domain for capturing dyes, for FRET with exogenously injected and bound fluorescent dyes.

Both voltage-sensitive domain-based and FRET rhodopsin-based GEVIs traditionally detected depolarizations as fluorescence decreases. Very recently, to require less light illumination intensity during periods of voltage responses and enable easier separation of signals from the low-intensity auto-fluorescence background, positively tuned sensors have also been developed. These include Positron (Abdelfattah et al., 2020), based on Voltron, and ASAP4 sensors (Evans et al., 2023), from the ASAP family.

Neurotransmitter Sensors and Watching Neurotransmission Over Space and Time

Starting in 2013 with iGluSnFR for detecting glutamate (Marvin et al., 2013), the development of genetically encoded fluorescent sensors for various specific neurotransmitters and neuropeptides has greatly increased. These sensors allowed for the real-time, direct observation of endogenous neurotransmission with millisecond and micrometer precision. Two main categories have been used for neurotransmitter sensors: 1) those utilizing bacterial periplasmic binding proteins (PBPs), which bacteria use to sense small molecules and neurotransmitters, as scaffolds, and 2) those using G-protein Coupled Receptors (GPCRs), which are endogenous transmembrane receptors for neurotransmitters and neuropeptides that eukaryotes use for cell signaling, as scaffolds.

PBP scaffolds are appealing because they undergo significant and consistent structural changes when they bind to specific ligands. PBPs consist of two parts connected by a hinge region with a ligand-binding site located between them. Then, intensity-based sensors for monitoring ligand changes in real-time are made by connecting the two PBP parts with a circularly permuted fluorescent protein (cpFP) in between the parts (Marvin et al., 2013). Using this design approach, sensors have been developed for glutamate, acetylcholine, GABA, nico-

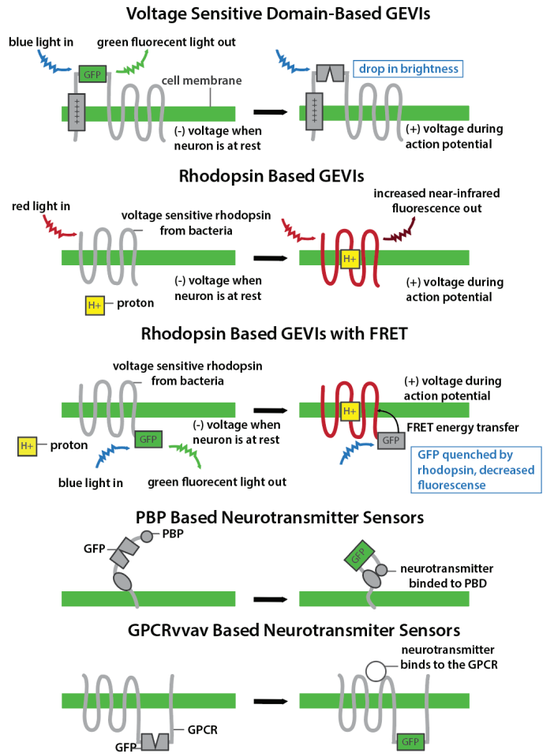

Fig. 10. Voltage sensors and neurotransmitter sensors

tine, ATP, glucose, and, most recently, serotonin.

On the other hand, GPCRs are the most extensive and varied category of membrane receptors within eukaryotes and are naturally expressed in the human/mouse brain. Current knowledge of GPCR structures suggests that the most significant structural change upon ligand binding occurs in the intracellular loop 3 (ICL3). Neurotransmitter sensors created by leveraging this conformational change and fusing cpFPs in this region include those for acetylcholine, norepinephrine, serotonin, adenosine, and ATP, in addition to neuropeptides endocannabinoids, somatostatin (SST), cholecystokinin (CCK), corticotropin-releasing factor (CRF), neuropeptide Y (NPY), neurotensin (NTS), and vasoactive intestinal peptide (VIP) (Wu et al., 2022).

Fluorescence Lifetimes and Absolute, Quantitative Measurements

Unlike traditional fluorescence microscopy, which relies on the intensity - number of photons - of emitted light, Fluorescence Lifetime Imaging Microscopy (FLIM) measures the time it takes for fluorophores to return to their ground state after being excited by a light source. While intensity-based fluorescence therefore depends on, and must be normalized for, fluorescent sensor expression and density, photon lifetimes do not depend on sensor expression or photobleaching. In this way, fluo-

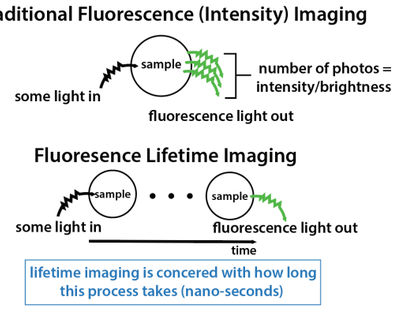

Fig. 11. Traditional vs lifetime microscopy

rescent sensors whose distributions of photon lifetimes depend on the absolute, quantitative concentration of their target molecule can be used to measure and compare across different sessions over any duration of time in any sample, regardless of how genetic transcription of the sensor or sensor degradation may have dramatically changed. Conversely, because shorter lifetimes will contribute to perceptions of higher intensity, many FLIM sensors can likewise be used as intensity-based sensors. Two markers of cellular respiration and metabolism, FAD and NADH, are endogenously auto-fluorescent, albeit at extremely short wavelengths of 450 and 340 nm, respectively. Interestingly, versions of the red Ca2+ indicator, RCaMP, already have Ca2+ concentration-dependent functions of fluorescence lifetime, despite not being originally developed with lifetime sensitivity in mind. Other deliberately engineered FLIM sensors have been made for Ca2+ (a turquoise one) (Van Der Linden et al., 2021), glucose (Díaz-García et al., 2019), and cAMP (Tewson et al., 2016), a secondary messenger for receptors.

Another common usage of FLIM is with FRET. The fact that FRET needs two fluorophores of different colors makes using these sensors with other sensors difficult (since two sensors of the same color cannot be used for intensity measurements), and intensity depends on relative fluorophore expression. However, as it turns out, donor fluorescence lifetime decreases when FRET occurs. FRET efficiency depends on how far away the acceptor and donor fluorophores are and therefore can be easily adapted for sensing either conformational changes in one protein or multi-protein-to-protein interactions. FLIM-FRET sensors include those for secondary messenger PKA and CREB, a transcription factor for plasticity (Laviv & Yasuda, 2021).

One limitation with FLIM is that since photon lifetimes are a probabilistic distribution, this must be fit or estimated to recorded photons for a measurement. FLIM therefore requires high numbers of accumulated photons to be accurate, and long periods of high-intensity light exposure are not ideal for cells, especially at UV ranges.

Discussion

In recent years, the landscape of neuroscience has undergone a transformative shift, with strategies for chemogenic control, electrical recording and control, optogenetics-based control, and optogenetics recording and visualization creating a diverse and robust toolset for understanding and driving functionally specific neural circuits in live animals. Basic metal electrodes are still used for clinical deep-brain stimulation (DBS), and early optogenetic opsins are just now being incorporated into clinical trials for vision restoration. Thus, advances in modern neurotechnology not only represent the potential for a greater understanding of neurobiology and behavior in animals but also the possibility for better, targeted therapeutics for more complex circuit-based neurological and psychiatric diseases in humans.

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