Analysis of the comparative strengths of intramural and extramural grant funding mechanisms

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Abstract

Science funders utilize a variety of funding mechanisms to advance scientific discovery, and the comparative strengths of these approaches are frequently debated. One prominent example is the contrast between extramurally funded research, where grants are awarded to external institutions, and intramurally funded research, where scientists are directly hired by funding agencies. Each mechanism is backed by theoretical justifications. In this context, we quantify the comparative strengths of the National Institutes of Health's extramural and intramural mechanisms. When adjusted for investment, extramural research excels at producing scholarly outputs such as publications and citations, which are standard metrics in academic assessment. In contrast, intramural research, whether basic or applied, stands out for producing research that influences subsequent clinical studies, aligning with its agency mission. These findings provide evidence that the institutional incentives associated with different funding mechanisms drive their comparative strengths.

Introduction

Knowing the efficiency of federally funded research is essential for responsible stewardship of public resources and maximizing the societal and economic impact of research investments. While the efficiency and return of federally funded projects have been examined at the levels of individual Principal Investigators (PIs) (Wahls, 2018b), research institutions (Wahls, 2018a), or specific funding programs (Azoulay, Zivin, & Manso, 2009), there is a lack of comprehensive knowledge regarding the overall efficiency of funders' investment portfolio.

Questions about the most effective approaches to structure portfolio management for science funders have been a source of contention. This is primarily due to the conflicting priorities among government officials, the mission of funding agencies, and the perspectives of scientific researchers (Goldstein & Kearney, 2020). While the 2018 Evidence Act (Abraham & Haskins, 2017; Young, 2021) mandates that all science funders incorporate data-driven decision-making, the U.S. Congress played a significant role in catalyzing such efforts, particularly at the National Institutes of Health (NIH), through the establishment of divisions such as the Office of Portfolio Analysis in 2011 (Department, 2011). The division was created to advance these data-driven initiatives even before they were broadly implemented across other federal agencies. Consequently, NIH serves as an excellent case study for policy examination, given its more extensive and robust data infrastructure compared to other agencies.

A pressing question that often surfaces, particularly when facing inflation-adjusted budgetary declines, concerns the comparative efficiency of externally funded grants, usually awarded to universities, medical institutions, and research centers, in contrast to intramurally funded projects where scientists are employed directly as government personnel and conduct research within federal facilities. The 2013 sequester (Fox, 2013), a budget reduction mechanism that abruptly removed a sizeable fraction of government funding for scientific research, revealed significant contention in the scientific community about the extent to which extramural versus intramural funding should shoulder the burden of budgetary declines (Drugmonkey, 2014).

Various theories exist to highlight the respective merits of these two funding models. Extramural institutions are thought to engage in extensive cost-sharing that might reduce the degree of government investment necessary to stimulate scientific advancement (Culliton, 1992; Korn, 2015; Macilwain, 1999). In effect, despite the negotiated indirect costs that are paid to offset institutional overhead that supports scientific research at extramural institutions, these institutions often contribute additional resources that foster science advance. Research indicates that institutional contributions, particularly in terms of trainee labor (Zhang, Wapman, Larremore, & Clauset, 2022), are important for stimulating scientific productivity, supporting this theory. Moreover, it is essential to recognize the substantial portion of extramural funding typically dedicated to training students and early career researchers. This investment not only aids in producing the next generation of researchers in the field but also contributes to the long-term sustainability of the research workforce (Harris, 2014). On the other hand, the direct hiring of scientists by the government under the intramural funding model allows for the selection of researchers whose research agendas more closely align with the agency's mission. Furthermore, despite shouldering the entire cost of intramural research, intramural PIs are freed from the time and resource burdens associated with grant applications. This freedom allows them to focus entirely on advancing scientific knowledge in their respective fields. Nonetheless, intramural grants may encounter constraints on autonomy due to their affiliation with a larger government institution, potentially restricting their freedom through manuscript clearance processes. This affiliation also implies that intramural researchers may not be entirely shielded from potential bureaucratic hurdles and unwarranted administrative burdens that can impede the progression of scientific endeavors. Therefore, each funding approach has unique strengths and considerations, making it essential to carefully weigh the advantages and disadvantages of extramural and intramural funding when allocating resources for scientific research.

Here, we investigate the comparative strengths of extramural versus intramural funding mechanisms for advancing scientific knowledge flow at NIH. Because the value of biomedical research is multifaceted, we employ a variety of measures. These metrics include traditional measures of scientific productivity such as investment-adjusted publication and citation rates, as well as predicted and realized knowledge diffusion into clinical studies that are aligned with the NIH agency mission. This study examined 98,648 research-oriented NIH projects funded after 2008 to examine the comparative strengths of intramural versus extramural projects. A total of 621,138 papers were published acknowledging at least one of these projects. We find that the comparative advantage of extramural projects is well-aligned with measures that reflect common assessment criteria in academia, such as generating publications and field-adjusted citations, both of which are important indicators of knowledge generation and knowledge flow. Intramural projects, despite seeming somewhat more focused on basic research, seem to have a comparative advantage at generating knowledge that informs downstream applied clinical work aimed at improving human health. This finding is consistent with a selection effect for intramural researchers whose agendas align more closely with the agency's mission.

Results

Research topic representation in Extramural vs. Intramural projects

One possible distinction between intramural and extramural funding mechanisms is that there may be differential selection effects in scientists' research agendas. Our examination of papers from intramural and extramural projects reveals differences from a high-level view of the research topics pursued by scientists funded under the two models. Based on unsupervised clustering of word2vec title-abstract embeddings, Figure 1 shows that intramural projects yield a higher-than-average number of publications pertaining to viral infection, cancer, and genes. Conversely, these intramural projects are underrepresented in research categories associated with adolescents, brain studies, and maternal health.

This result may signal a different prioritization in resource allocation and topics within research institutions. The emphasis on areas like viral infection and cancer in intramural projects could potentially indicate a strategic alignment with prevalent global health challenges. Notably, the viral infections & immunity category of intramural research was critical for the rapid development of COVID-19 vaccines. In addition to contributing directly to the Moderna mRNA vaccine that contributed to the 2023 Nobel Prize (Callaway & Naddaf, 2023; F. Collins et al., 2023; Fauci, 2021), intramural vaccine research into the mutational stabilization of prefusion proteins was used by other organizations in their COVID-19 vaccine development (Fauci, 2021).

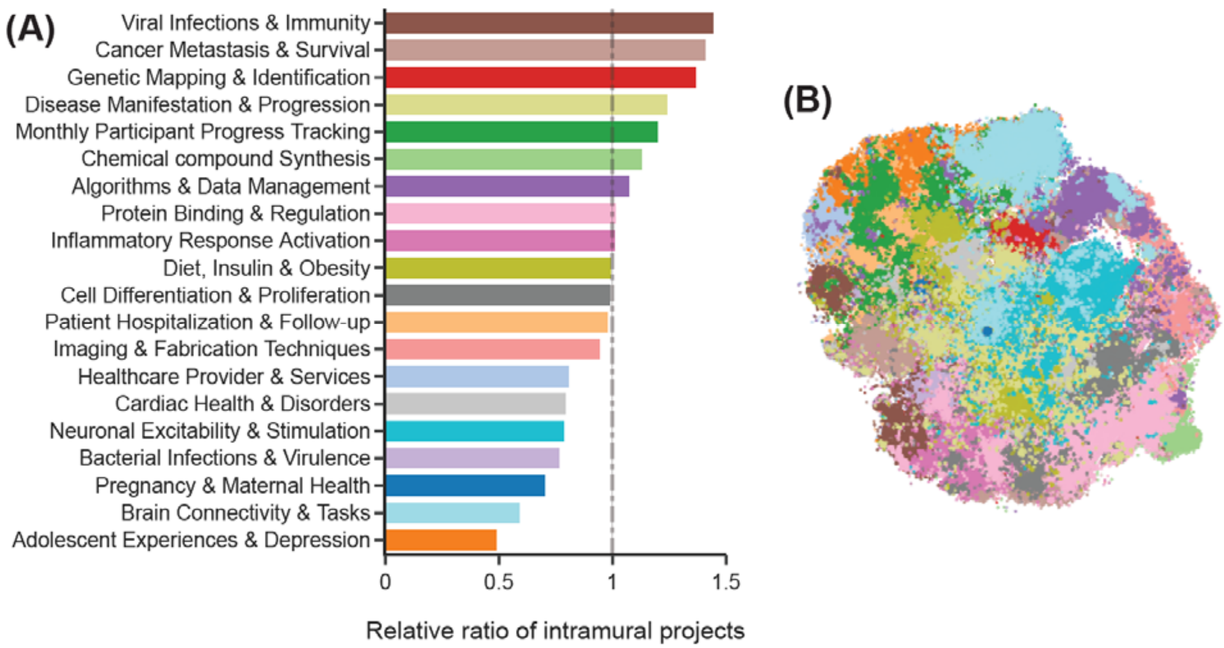

Figure 1. Research topics of intramural and extramural projects. Topics were identified by clustering publications based on their titles and abstracts via Word2Vec. **(A)** Relative ratio of intramural projects per topic cluster. A relative ratio exceeding 1 signifies a higher share of intramural project publications in that topic relative to their share across all topics. **(B)** T-SNE plot illustrating the distribution of topic clusters, with colors consistent with those in (A).

Level of investment for intramural and extramural projects

A second way to characterize the differences between intramural and extramural funding is by looking at federal investment. While extramural research institutions do receive audited indirect costs to cover overhead associated with research, recent research indicates that significant cost-sharing greatly influences scientific productivity on federally funded research. Specifically, the extent to which universities subsidize the labor costs of students is a direct factor in the varying levels of productivity among institutions (Zhang et al., 2022). This raises the possibility that dollar-for-dollar, extramural research may be more cost-effective as a direct result of cost-sharing not reflected in indirect costs awarded to extramural institutions.

Our data demonstrate that intramural and extramural projects receive highly differentiated funding every year. In our data, 59.3% of extramural projects received less than $1 million in accumulative total funding, while only 28.8% of intramural projects received less than $1 million. Accounting for variations in the funding year duration, extramural projects consistently received lower annual funding than their intramural counterparts. At the same percentile, the annual funding for extramural projects is consistently lower than for intramural projects. Moreover, every year, not only does the average spending on intramural projects exceed that of extramural projects, but it also increases at a swifter pace. This finding is consistent with the concept that intramural research may demand higher financial commitment due to the absence of cost-sharing with external institutions. It also mirrors prior observations that extramural researchers may increasingly need to procure multiple federally funded grants to sustain an extramural research lab.

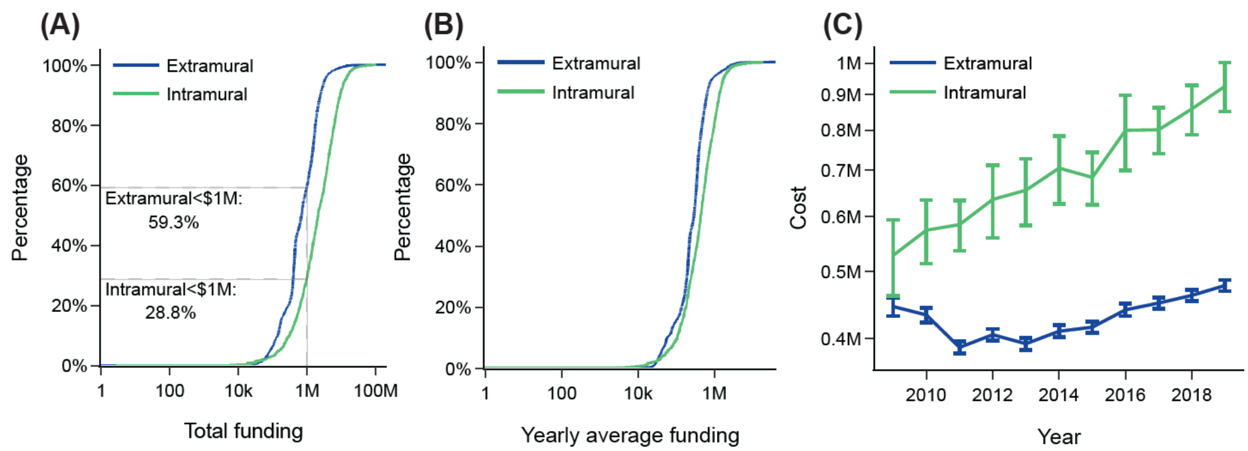

Figure 2. Project funding for intramural and extramural projects. (A) Cumulative percentage of projects by each project's total project funding. Total funding amounts on the X-axis are in log scale. **(B)** Cumulative percentage of projects by each project's average annual fundings. **(C)** Average project costs by years from 2009 to 2019. Error bars denote 95% confidence intervals.

Outcomes of intramural and extramural projects

We then delved into the potential distinctions in research outcomes between projects funded intramurally versus those funded extramurally. To evaluate the multi-dimensional research outputs of NIH projects, we quantified the performance of research outputs using five metrics based on produced papers: number of papers, relative citation ratio (RCR, a field- and time-normalized measure of scientific influence (B. I. Hutchins, Hoppe, Meseroll, Anderson, & Santangelo, 2017; B. I. Hutchins, Yuan, Anderson, & Santangelo, 2016)), approximate potential to translate (APT, a machine learning prediction that a given paper will be cited by a clinical article (B. I. Hutchins, Davis, Meseroll, & Santangelo, 2019)), realized total clinical citation counts (B. I. Hutchins, Baker, et al., 2019; B. I. Hutchins, Davis, et al., 2019; iCite, Hutchins, & Santangelo, 2019), and a binary measure of the number of papers that received at least one clinical citation. All these are metrics at the article level. For a more comprehensive perspective, we tallied these metrics annually, summing up the papers published within each year. By plotting the annual trends of average research output per project, we found that intramural projects had a noticeable edge over extramural ones at early stages (Figure 3). For example, on average, one intramural project published 1.53 more papers than one extramural project. However, this disparity between intramural and extramural projects seemed to diminish as time progressed.

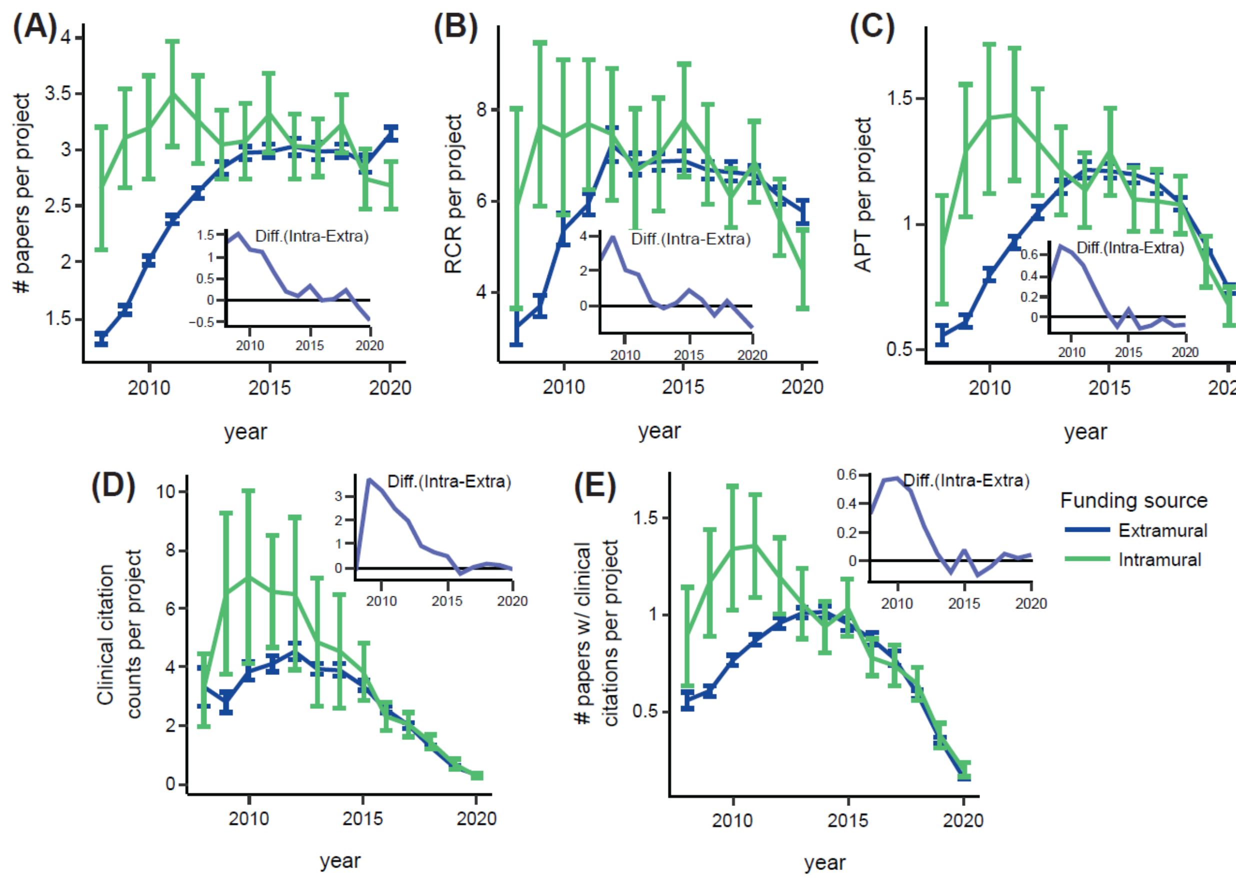

Figure 3. Intramural and extramural projects' research output by year. (A)-(E) Average number of papers (A), RCR (B), APT (C), total clinical citation counts (D), and number of papers once received clinical citations per project (E) by year. Error bars denote 95% confidence intervals.

Cost efficiency of intramural and extramural projects

Based on these descriptive statistics, intramural projects appear more productive. Yet, it is essential to note that the levels of investment vary between intramural and extramural projects (Figure 2). When accounting for the level of investment, the perceived efficiency of intramural projects may not be as pronounced due to the higher funding they receive per project (Figure 2). Calculating the investment needed to generate each type of research output can reveal relative research efficiencies of the project mechanisms. Here, we utilize an inflation-adjusted investment-to-output ratio to represent the average investment needed for each unit of research output. The ratio for one specific year is the ratio of the inflation-adjusted cumulative investment to the cumulative research output. Importantly, it is noted that authors often continue to publish papers for many years after a grant has ended (Supplemental Table 1). To account for this, grant amounts were multiplied by a deflator— this represents the proportion of papers published to date against the anticipated number of future publications, as determined by empirical measurements.

As shown in Figure 4, the investment-to-output ratio rose during the funding years and then plateaued once the funding concluded. Considering the number of papers, RCR, and APT (the first three rows of subfigures), it's evident that, for the majority of the time post-funding initiation, intramural projects exhibited higher cost-to-output ratios than their extramural counterparts. However, for projects with a funding duration of fewer than six years, extramural projects appear to match or even surpass intramural projects in terms of average investment-to-output ratios. This finding suggests that intramural projects with short to medium durations may be more adept at accumulating clinical citations compared to extramural projects. In contrast, extramural projects, based on this preliminary analysis, may require less investment for several metrics and show potential for long-term influence, exhibiting their own distinct advantages in producing long-term impact.

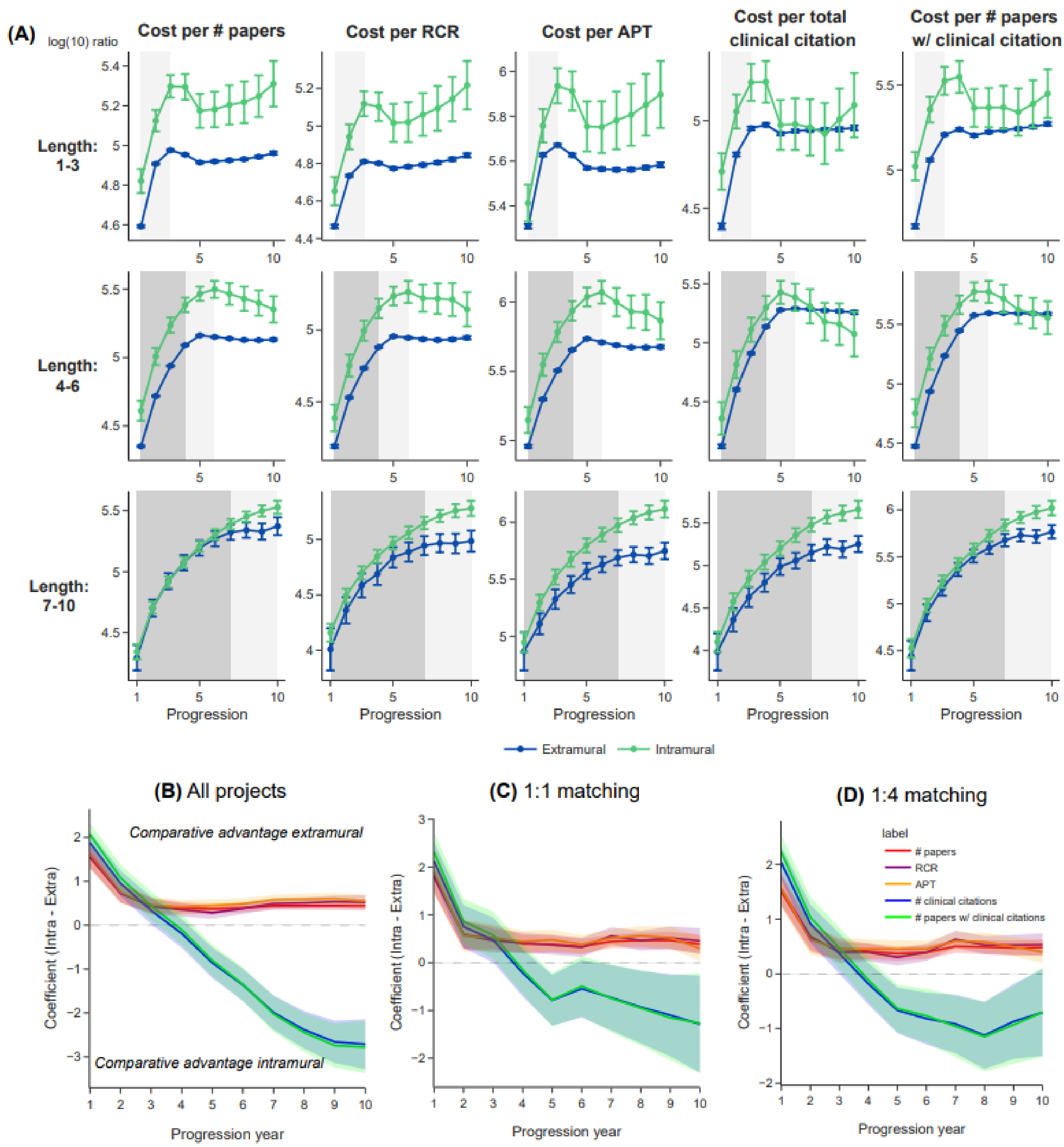

Figure 4. Project efficiency analysis. (A) Average deflated cost-to-output ratio over the years, categorized by project types and funding year length. The Y-axis displays the base-10 logarithm of the

raw cost-paper ratio increased by one. Error bars denote the 95% confidence intervals. The funding year lengths are highlighted by the gray-shaded regions, with light gray indicating the possible ending funding year. **(B-D)** Linear regression results of research output measures against project types. The regression model was fitted for each year of the project's progression. The Y-axis coefficient indicates the mean disparity in research output between intramural and extramural projects, controlling for other variables. Separate regressions were conducted for all projects (B), and for balanced projects using 1:1 (C) and 1:4 (D) propensity score matching.

Aggregate descriptive statistics provide valuable insights into the comparative strengths of the intramural and extramural funding mechanisms. However, these cannot rule out the possibility that other project features contributed to the difference between intramural and extramural projects. For example, human-focused research has higher regulatory overhead costs due to increased ethical concerns. Likewise, animal research is more expensive than cellular biology research. To take these variables into account, we conducted a regression analysis with comprehensive controls for features about the PI's historical research patterns and project topic, aiming to explore the relationship between project type and research output. The results in Figure 4B-D show that extramural projects have a higher average output-to-investment ratio when measured by the number of papers, RCR, and APT throughout the progression years. However, when measured by clinical citation counts and the number of papers with clinical citations, we found that intramural projects exceeding four years in duration tend to become more efficient than extramural projects of equivalent length.

To further enhance the comparability of the two project types, we performed propensity score matching between the two groups of projects based on their features. This method involved pairing each intramural project with its closest extramural counterparts—first with one, then with four—based on their calculated propensity scores. We then applied linear regression to this more balanced sample set. These combined results demonstrate that the comparative strengths of extramural funding mechanisms are well-aligned with traditional academic measures of knowledge generation and flow, while intramural mechanisms appear to be more in tune with generating research that translates to downstream clinical knowledge in line with the agency mission.

One possible explanation for these results is that there may be more human focus in intramurally funded research that could explain the differences in clinical citations. In particular, the NIH intramural Clinical Center might account for such an effect. Longer-duration grants may show the most significant effect in such a case, since human clinical work may take longer to conduct by its nature. As shown by Figure 5, both intramural and extramural projects have the highest average scores in the human aspect of their papers. However, long-duration intramural projects tend to have lower human scores, while long-duration extramural projects tend to have higher human scores. For animal and molecular-cellular scores, the trend is reversed. Long-duration intramural projects tend to have higher animal and molecular-cellular scores, while long-duration extramural projects tend to have lower scores. The possibility that longer-term intramural projects are more human-focused, which might explain the clinical citation comparative advantage with respect to the extramural program, is therefore inconsistent with the data.

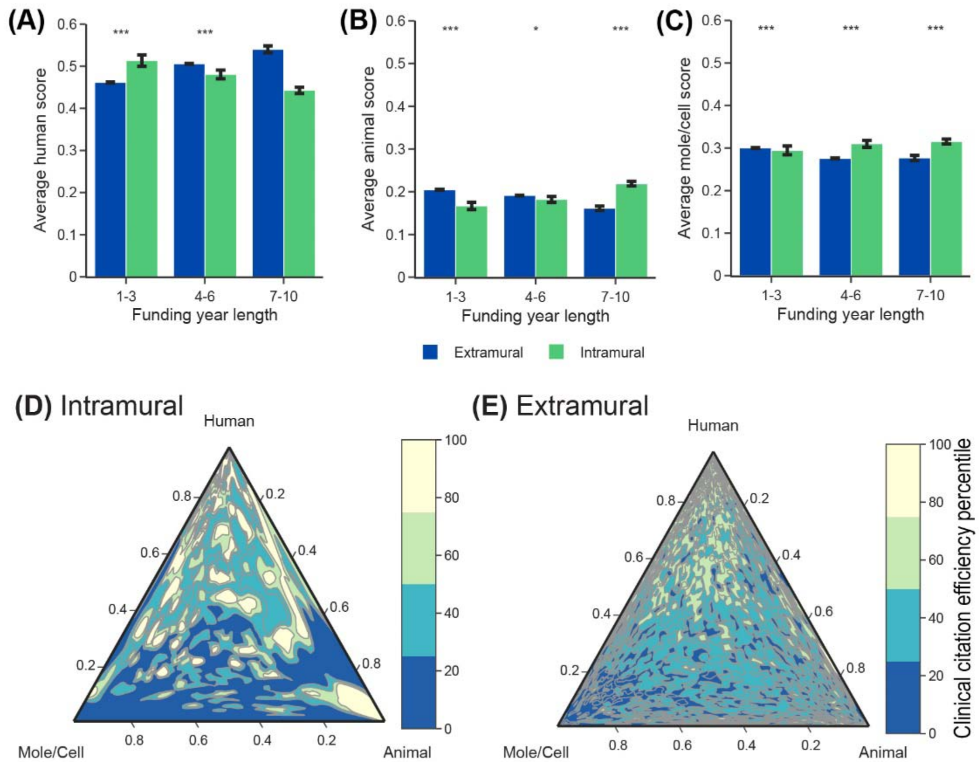

Figure 5. Comparison of human, animal, and molecular/cellular scores between intramural and extramural projects. A project's scores were calculated by the mean scores of its publications. **(A)-(C)** Projects' average human (A), animal (B), and molecular/cellular (C) scores by funding year lengths. Mann-Whiteney U tests were conducted to test the score difference between intramural and extramural projects. *** p<0.001, ** p < 0.01, * p < 0.05. **(D)-(E)** Ternary contour plots representing the clinical citation efficiency in the human, animal, and molecular/cellular score system for intramural (D) and extramural projects (E). Here, efficiency was the percentile of the cost-to-output ratio in descending order. Each contour line denotes a constant efficiency percentile. Yellow/green are high-efficiency areas of the triangle, and blues are low-efficiency areas.

To further explore this gap, we conducted a term-frequency analysis of the abstracts of intramural versus extramural awards. We observe that extramural research tends to be couched in languages supporting the pursuit of mechanistic discoveries (Figure 6). Intramural research, by contrast, seems to be more goal-focused and disease-oriented.

Figure 6. High-frequency words in intramural and extramural projects' abstracts by funding year lengths (L).

Discussion

Taken together, these results demonstrate comparative advantages for extramural and intramural funding mechanisms. In particular, extramural funding seems to excel at generating raw knowledge and facilitating its downstream flow. In contrast, intramural funding mechanisms seem to have a comparative advantage at generating research, basic or human-focused, that successfully informs downstream clinical research, aligning with the agency's mission. This could potentially be attributed to the selection process for directly hiring scientists whose research agendas closely match the agency's objectives, though this aspect wasn't directly assessed in our study. However, we do rule out an obvious explanation: that more human-focused work in the intramural program is more likely to be conceptually closer to clinical trials and, therefore, have a lower barrier to entry into clinical studies (Kim, Levine, Nehl, & Walsh, 2020;

Weber, 2013). Intramural research is characterized by long-duration projects in contrast to the extramural portfolio, and these appear less human-focused than the extramural portfolio.

Critiques of NIH's grant review process often cite its conservatism, with a strong emphasis on preliminary data to mitigate project failure risks (Packalen & Bhattacharya, 2020). The recent creation of the Advanced Research Projects Agency for Health (ARPA-H) was in part for this reason (F. S. Collins, Schwetz, Tabak, & Lander, 2021). Although the high-risk, high-reward NIH portfolio seems to be largely effective at identifying and funding such projects (Tabak et al., 2019), its overall proportion of the total portfolio remains relatively small in favor of more traditional investigator-initiated research project grants. Because intramural researchers face retrospective rather than prospective review, this conservatism might be expected to manifest in a comparative advantage across a variety of measures for intramurally funded research. Competing theories suggest that extramural research may hold advantages on an investment-adjusted basis because of cost-sharing at universities, particularly for student labor (Zhang et al., 2022). Notably, Intramural research focused on human/molecular or animal research seems to be particularly effective at generating clinically relevant research outputs (Figure 5). Our findings reveal a nuanced reality: extramural institutions hold an edge in publication and citation rates aligned with their internal review procedures, while intramural research excels at stimulating bench-to-bedside translation on an investment-adjusted basis.

This study is not without limitations. First, data about the intramural portfolio is only available from post-2008, which constrains the time frame for this study. Second, collaboration between intramurally and extramurally funded scientists introduces complexity to the comparative analysis, leading to the exclusion of jointly funded publications. Finally, while some quantitative indicators have achieved parity with expert reviews in terms of inter-rater reliability or positive predictive value, they do not fully encapsulate the value of research. For that reason, we included a panel of multifaceted quantitative measures to investigate multiple facets. Our results highlight distinct comparative strengths of both extramural and intramural funding mechanisms, reflecting the divergent incentives tied to academic versus agency missions inherent to each funding type.

Data and methods

Data

We collected the original NIH project data from NIH RePORTER (Health, 2021), which contains 433,930 projects with funding information spanning from 1985 to 2019. We identified projects' activity categories by looking up their first three letters in the project number (activity code). We classified the projects into intramural and extramural projects by the initial letter of their activity codes. Specifically, projects with an activity code starting with Z were intramural projects, and other projects were extramural projects. Using this strategy, we identified 9,225 intramural projects and 424,705 extramural projects in the raw dataset. We retrieved the publication records for these projects by PMID indexed by PubMed (Medicine, 2020).

The data cleaning process is as follows. First, as the renewal of project contracts may alter the topic and arrangement of the projects, we dropped 70,297 projects with renewal records in our data. Second, considering intramural projects might change their activity categories and the three initial project number letters (e.g., ZIA changed to ZIH), we normalized 3,105 intramural project numbers by matching the rest of the project numbers to avoid inconsistency in project numbers. Third, to focus on activity categories intended as research-oriented and exclude practice-oriented activity categories, at the activity level, we selected activity categories where at least 75% of projects had produced at least one paper. This step kept 106 activity categories (including six intramural activity categories).

In this study, we focus on projects initially funded after 2008 and select the ten years from 2009 to 2019 as our analysis period. A total of 122,815 projects fell in this period. To remove the rest of potential non-research-oriented projects, at the individual project level, we selected 1% of projects with the highest cumulative ratio of funding and publication number and 1% of projects with the lowest. We then trained a random forest model to predict the projects most likely to be non-research-oriented based on their title and abstracts. Based on the predicted probability, we excluded 5% of intramural (84) and extramural (5,347) projects. We also excluded 18,736 projects that had no publications or published papers before the funding started. The final analytical sample consists of 98,648 projects, including 97,054 extramural projects and 1,594 intramural projects, which produced 621,138 papers during our time window.

Cost-to-output ratio

We used the primary project costs listed on NIH RePORTER as the cost data source. Subproject costs were not calculated. Given the influence of price changes and inflations over years, we converted all funding costs at the 2015 price level using NIH's Biomedical Research and Development Price Index.

We used five paper-level metrics to measure the research output: number of papers, relative citation ratio (RCR) (B. I. Hutchins et al., 2017; B. I. Hutchins et al., 2016), approximate potential to translate (APT) (B. I. Hutchins, Davis, et al., 2019; Santangelo, 2017; Weber, 2013), total clinical citation counts (B. Ian Hutchins, 2021; B. I. Hutchins, Baker, et al., 2019; iCite et al., 2019), and number of papers once received clinical citations. A project's total research performance regarding a certain metric in one year is approximated as the sum of that metric for every paper published in that year.

Based on the project costs and research outputs, we calculated the cost-to-output ratio as follows.

$$R_{ij} = \frac{C_{ij}}{O_{ij}} * \frac{P_{ij}}{TP_i}$$

Where $\mathrm{R_{ij}}$ is the cost-to-output ratio for project i in year j, $\mathrm{C_{ij}}$ the cumulative sum of funding costs for project i up to year j, $\mathrm{O_{ij}}$ is the cumulative sum of a certain research performance metric for project i up to year j, P_{ij} is the cumulative number of papers for project i up to year j, and TP_i is the total number of papers for project i until 2020.

Regression analysis

We run the following regression model at the project level to estimate the differences between extra- and intramural projects for every year after the projects started.

$$\log(y_{it} + 1) = \beta_0 + \beta_1 I_i + \beta_2 T_t + \sum \beta p_i + \alpha\, r_t + \delta s_i$$

where y_{it} is project i's deflated cost efficiency regarding a certain research performance t years after the funding start year; I_i is whether project i is an intramural project (1 if yes); T_t is the length of funding years until that time point, equal to the minimum of t and the total funding years; p_i stands for the PI-related variables; r_t and s_i are the year's and project topic's fixed effects. We transformed the y_{it} into $\log(y_{it} + 1)$ to mitigate the impact of uneven distribution.

PI-related variables include the number of past publications, number of past projects, number of PIs, share of clinical papers, past publications' average relative citation ratio, publication experience, project experience, number of collaborators. We downloaded the PubMed Knowledge Graph datasets (Xu et al., 2020) to help extract the PI level variables. The dataset has disambiguated the authors of PubMed indexed publications and assigned unique identifiers to the authors. We matched both project numbers and paper author names with the datasets to find the PI's assigned unique identifiers. We successfully retrieved the PI information for 98803 (94.9%) projects. The PI-related variables before the project funding started were extracted for every project, which played the proxy role of the input for the projects.

Another control variable, project topic, is calculated by performing a K-means clustering based on the NIH spending categories for all the projects in the sample. To restrict the dimensionality, the 100 most frequent NIH spending categories were used in clustering, which cover 96.4% of all projects. We tried k=3, 4…10 and finally selected k=5 which generated the highest silhouette score.

As a robustness check, we used propensity score matching to reduce the potential confounding biases that may affect the outcome of interest and increase the comparability between intra- and extramural projects. For every year after the projects started, we used all project-level variables, including the length of funding years until that time point, PI-related variables, and project topics, to predict the propensity score of each project by fitting a logistic regression model. The propensity score shows the probability of a project to be an intramural project, based on the observable variables. For each intramural project, we selected one and four extramural projects, respectively, with the nearest propensity scores from a pool of extramural projects with the same funding start year. The regression model was run on the PSM sample again to check the robustness of previous results.

Paper features

We used the concatenated documents of a paper's title and abstract to train a word2vec model (Analysis, 2018; Analysis, Intelligence, & Institute, 2019; Hoppe et al., 2019) to classify the papers into clusters. We removed common stop words, punctuation, and content lacking semantic information before training. During clustering, each paper's document is represented as a 300-dimension vector by summing its each unique word's vector weighted by its IDF. Principal component analysis (PCA) dimensionality reduction is applied to these 300-dimensional vectors to identify the 25 most influential components. We finally performed spectral clustering method using the document vectors and extract highly-frequent words to determine the cluster property and labels. Word2Vec nearest neighbor terms were uploaded to ChatGPT to develop more human-readable labels.

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