Evaluation of the P01 Portfolio at the National Institute on Aging

Prepared by the NIA Office of Policy, Analysis, and Evaluation & Abt Associates Inc.

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Purpose and Approach

The purpose of this evaluation is to learn how NIA can maximize return on investment by improving the way in which we use the P01 funding mechanism in accomplishing our mission and goals. This evaluation is the first of a series of planned assessments to better shape future initiatives and inform funding decisions.

The approach used for this evaluation included initial discussions with extramural division representatives to identify their objectives and hoped-for outcomes from the use of this mechanism, portfolio analysis, bibliographic analysis, program officer interviews, and reviews of abstracts. Each of these is described below. These activities were carried out by NIA Office of Planning, Analysis, and Evaluation staff and with assistance from an independent research firm Abt Associates.

Initial Discussions with Extramural Division Representatives

The evaluation team met with extramural division representatives on February 22, 2010, to learn from staff what they hoped to gain from research funded through the program project grant mechanism (P01). The division groups identified eight types of outcomes that they hope to achieve by funding research using the P01 as opposed to other mechanisms such as R01s, Center programs (P30s and P50s), cooperative agreements (U01s), or Funding Opportunity Announcements (FOAs). They hope to:

- Promote interdisciplinary science.
- Facilitate high quality research.
- Jumpstart new areas of research.
- Provide needed infrastructure to support large, complex research projects.
- Move science along the translational/translation continuum.
- Attract top researchers to aging research, especially in areas not typically viewed as aging related.
- Build relationships for future collaboration.
- Provide mentoring opportunities.

Some participants also indicated that the P01 allows for an easier review process. Within each of these outcome areas, division representatives identified evaluation questions and related measures they believed would be important to address. See Appendix A for the full listing of responses from these sessions.

Portfolio Analysis

We collected and examined data on 210 NIA-supported P01 grants funded over the past 20 years (1990-2009) along with data on 81 R01 grants of over $1M/year and 120 U01s for the same time period for comparison purposes. These data include:

- Total funding for each of the three mechanisms in relation to the total NIA RPG line
- Comparison of returns on investment (cost per publication) across the three mechanisms

- Numbers and funding amounts for the three types of funding awarded during the time period broken down by division/program
- Percentages of the total NIA and division portfolios and funding amounts that the three types of awards represent
- Variety of scientific disciplines represented within each Division such as immunology, behavioral research, neuropsychology, clinical research

Review of Abstracts

We reviewed abstracts to identify:

- More information on the interdisciplinary makeup of the teams – what disciplines, what types of organizations, etc.
- Example descriptions of services provided by cores including administrative activities – e.g., facilitation of team interactions, scientific guidance – and the development of various research resources – e.g., databases, animal models, biospecimen repositories.
- References to/descriptions of publications, patents, clinical trials, etc.

Interviews with Program Officers

Interviews with program officers were a critical component of this evaluation and provided considerable insights into how the Divisions perceive and use the P01 mechanism. Listed below are examples of the types of information that were collected through these interviews.

- Anecdotal success stories and examples of exemplary interdisciplinary teamwork, infrastructure, or leadership
- Suggestions of new/emerging areas that might be tracked to P01s
- Especially significant examples of interventions coming out of P01s with explanations as to why they were deemed successful
- Significant examples of how P01s have been instrumental in drawing top scientists or young investigators to the field of aging research

See Appendix B for the full list of questions included in the interview protocol.

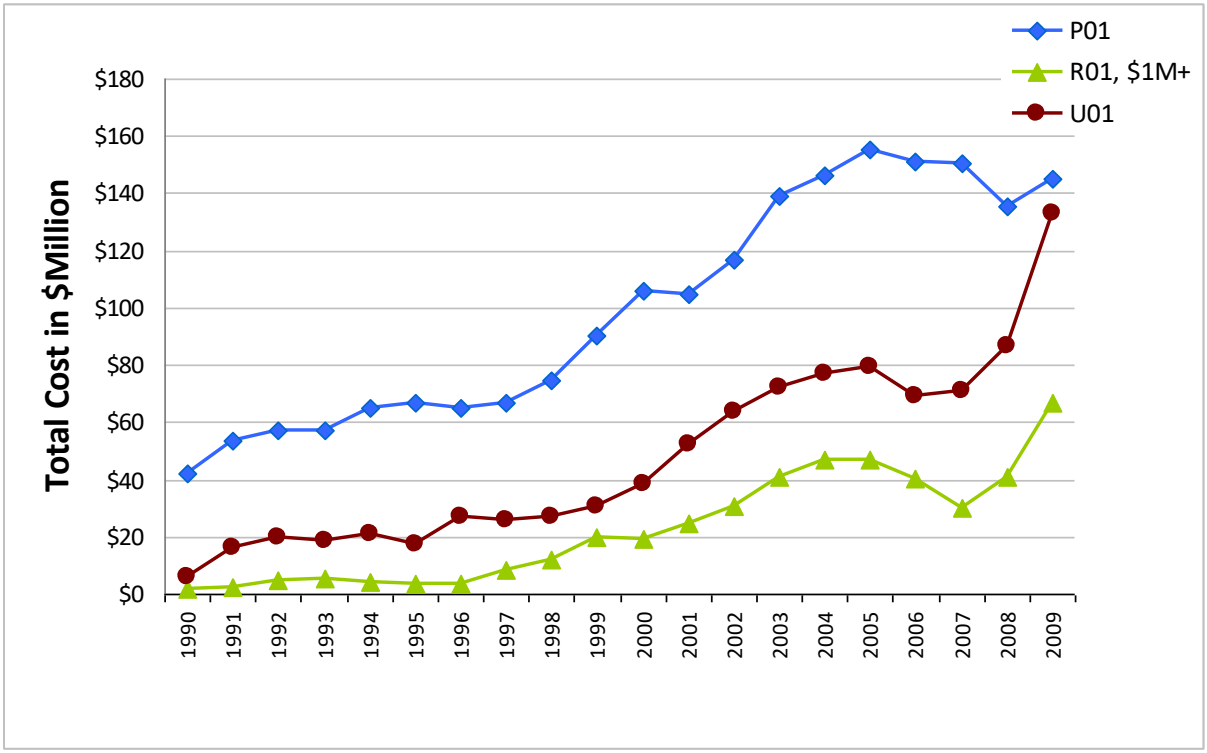
Findings

In this Chapter, we summarize our key findings.

P01 Funding Information at NIA and by IC

Exhibit 1 shows the total costs of P01s, large R01s, and U01s for the past 20 years in unadjusted dollars. Expenditures for all three mechanisms follow the same trend of steady growth with a dip from FY2005 to FY2007. During the entire time period, P01 spending was higher than large R01 or U01 grants and exceeded $140 million in FY2009.

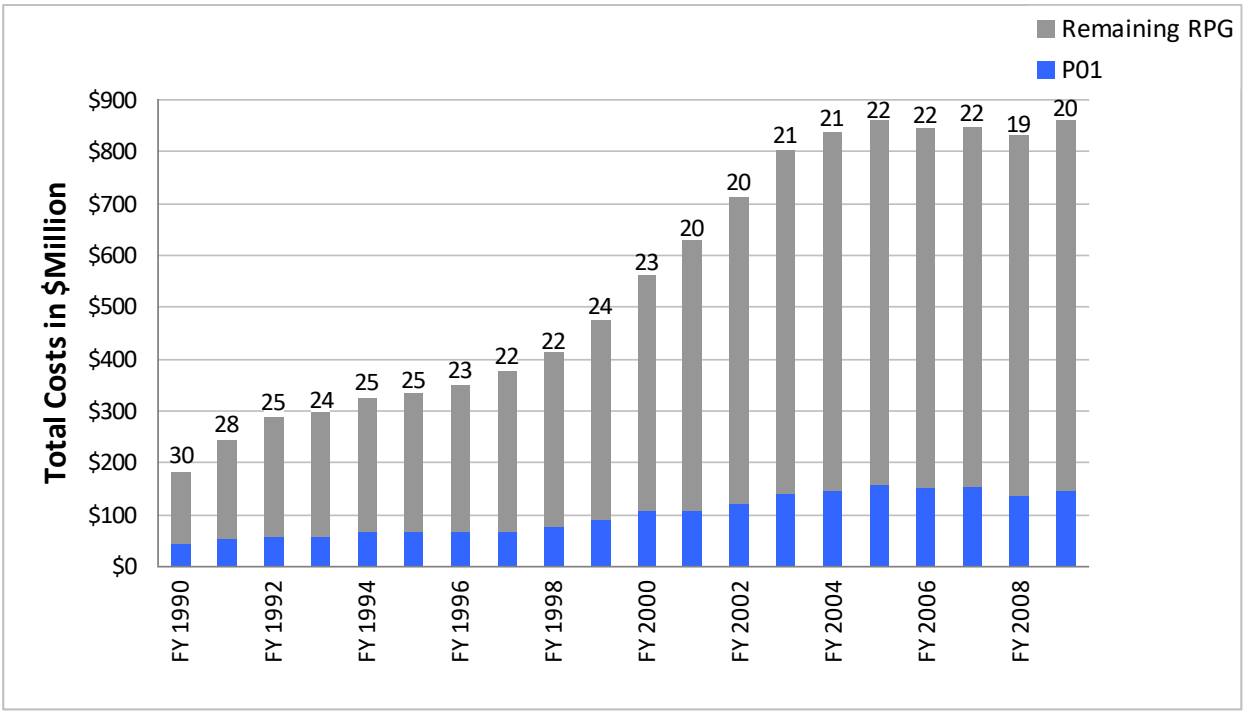
Exhibit 1: Total Costs for P01, R01, and U01 Funding by Fiscal Year at NIA, FY1990-2009



Data Source: QVR
R01 data includes only those grants at $1M or more per year

While the total funding for P01s has grown over time (Exhibit 1), total expenditures for this grant mechanism relative to the total NIA research project grant (RPG) line have decreased from 30% in FY1990 to 19-20% in FY2008-2009 (Exhibits 2 and 3). This trend was in contrast to large R01 and U01 expenditures, which grew from 1% to 9% for large R01s and from 4% to 19% for U01s.

Exhibit 2: P01, U01, and Large R01 Total Costs Relative To Total NIA RPG Line



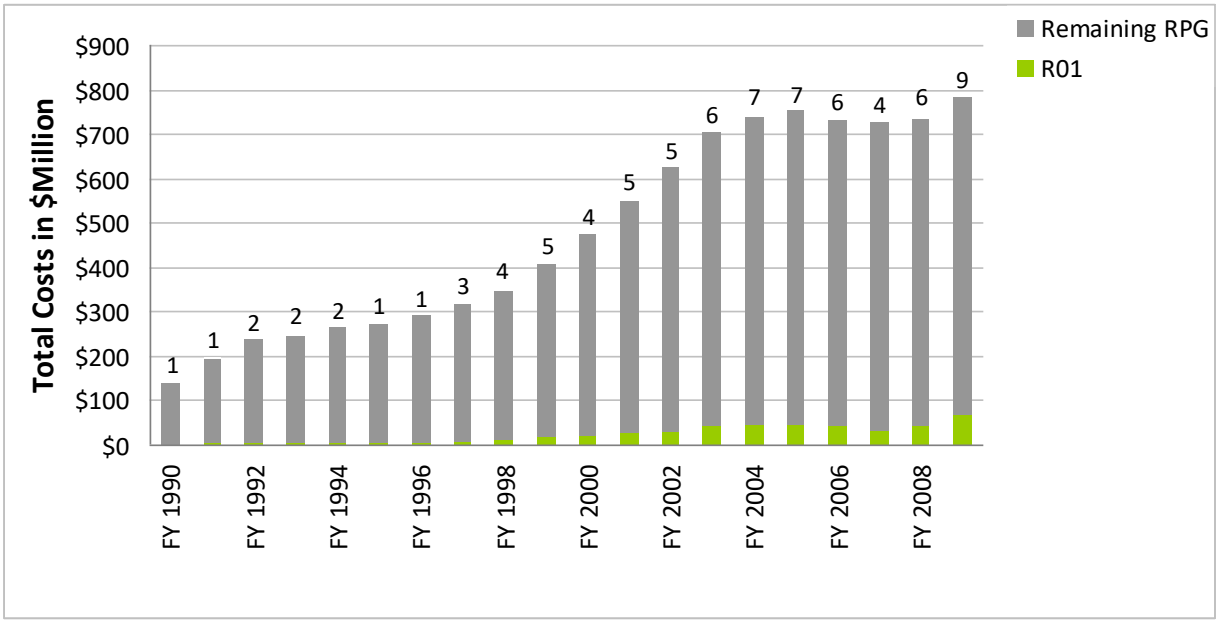


Exhibit 2: P01, U01, and Large R01 Total Costs Relative To Total NIA RPG Line

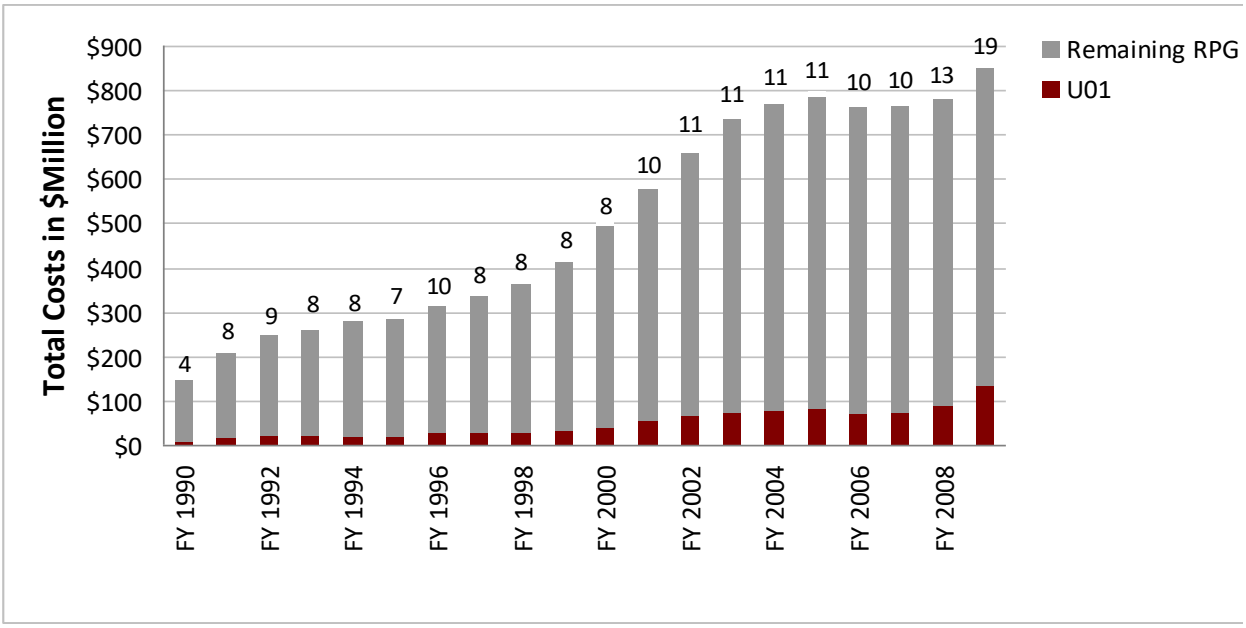
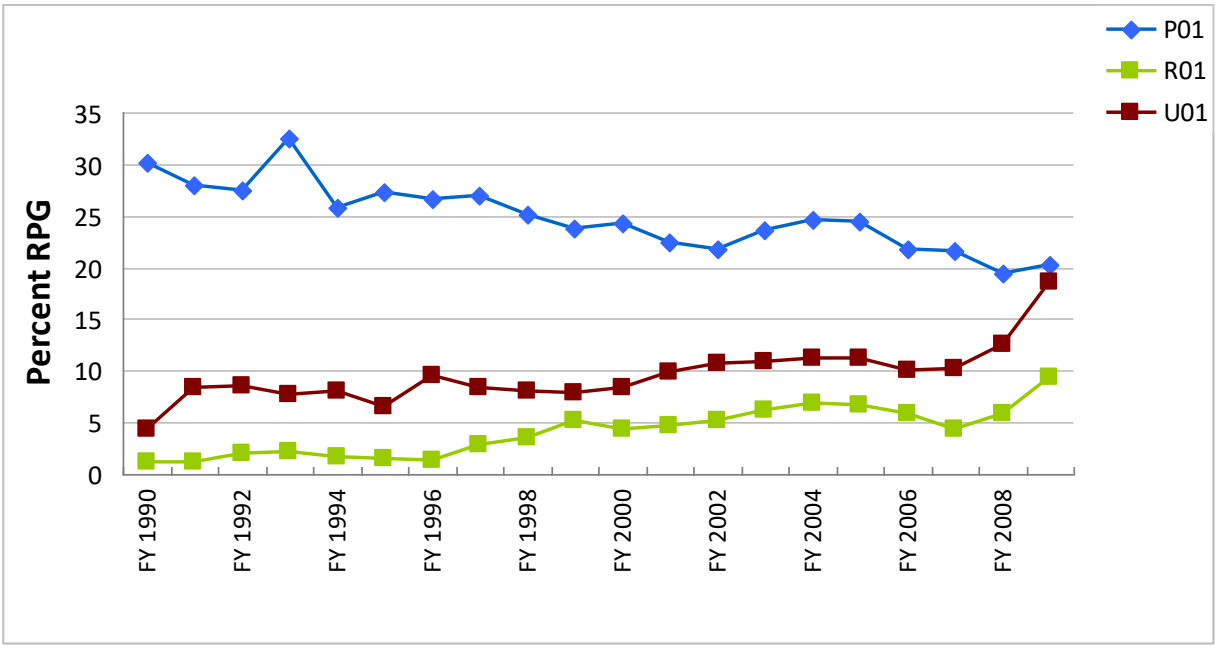


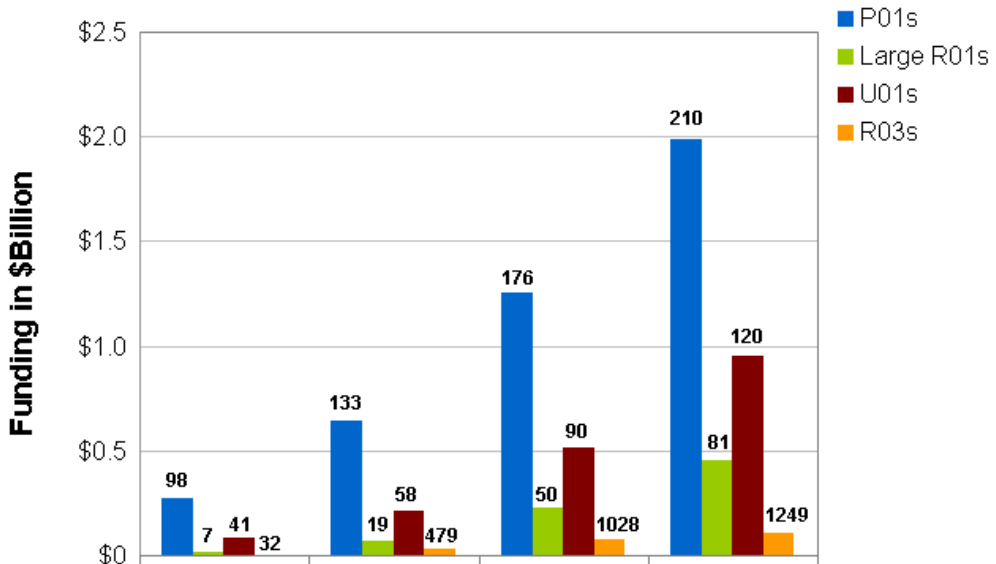
Exhibit 3: P01, R01 ($1M+/yr), U01 Total Costs as Percent of Total NIA RPG Line



Data Source: QVR

Exhibit 4 shows the cumulative total costs for P01s, large R01s, U01s, and R03s over four periods of time spanning the past 20 years. Numbers located above the bars indicate grant counts. All four mechanisms received increased amounts of funding over time, with P01s consistently exceeding the other three mechanisms examined.

Exhibit 4: Five-, Ten-, Fifteen-Year Cumulative Funding by Grant Mechanism at NIA, FY1990-2010

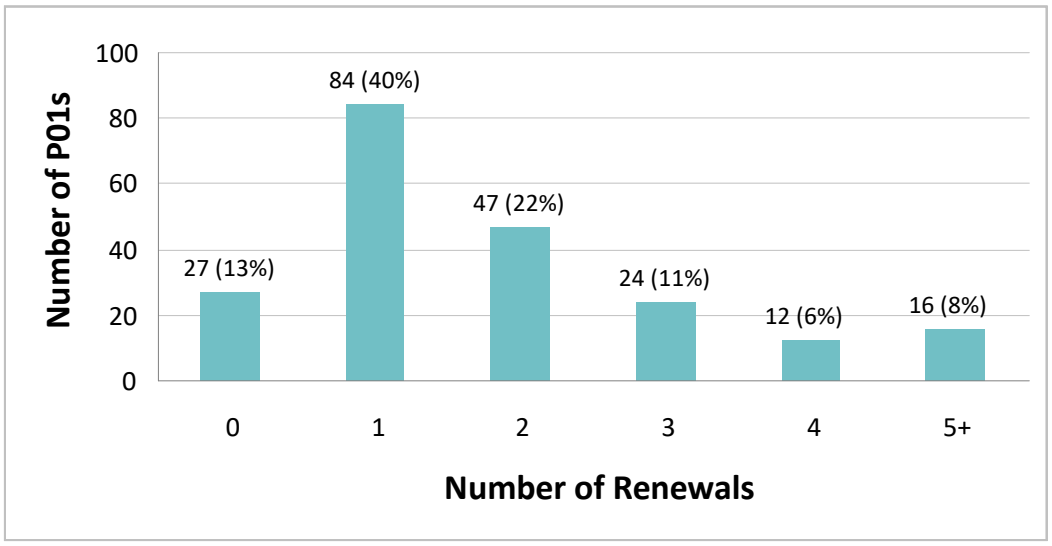


	FY1990-1994	FY1990-1999	FY1990-2004	FY1990-2009
P01s	$275,300,446	$638,554,904	$1,252,021,117	$1,988,995,344
Large R01s	$18,172,031	$66,233,858	$228,776,314	$453,557,877
U01s	$81,112,403	$209,701,400	$513,573,928	$953,493,374
R03s	$775,870	$32,048,398	$73,557,831	$104,587,524

Data Source: QVR

Exhibit 5 shows the breakout of the 210 P01s included in this evaluation according to number of times renewed over the assessment time period. The numbers of renewals, identified at five-year intervals, were determined based on the project start and end dates.

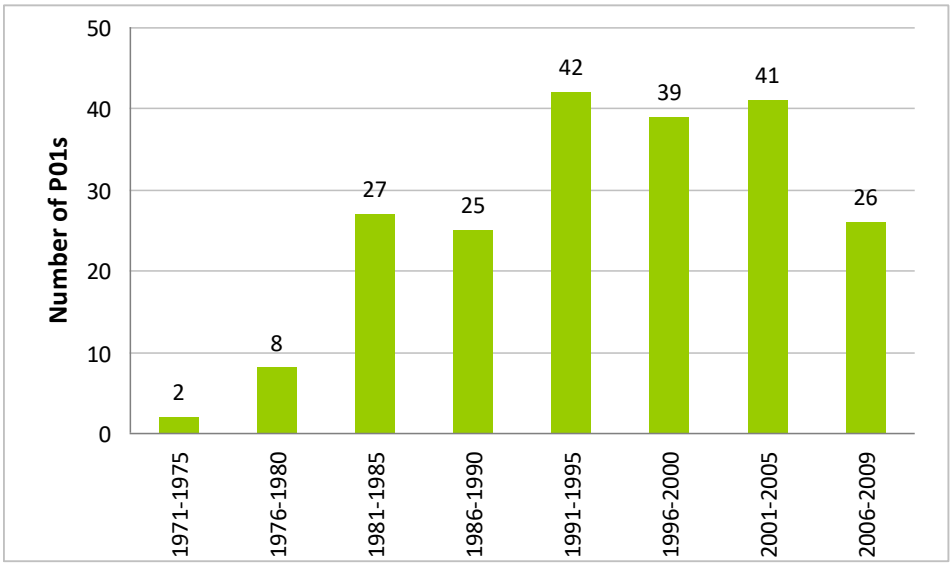
Exhibit 5: P01s by Number and Percent of Renewals at NIA



Data Source: eSPA

Using the start dates for the 210 P01s included in this evaluation, the chart below indicates the growth of P01s over time in 5 year increments.

Exhibit 6: Number of P01s by Start Date



Data Source: eSPA

Exhibits 7 and 8 show the total costs of P01 grants by IC for selected years. NIA ranks among the top 5 in terms of funding levels for P01s.

Exhibit 7: P01 Total Costs by Institute and Center for Selected Years

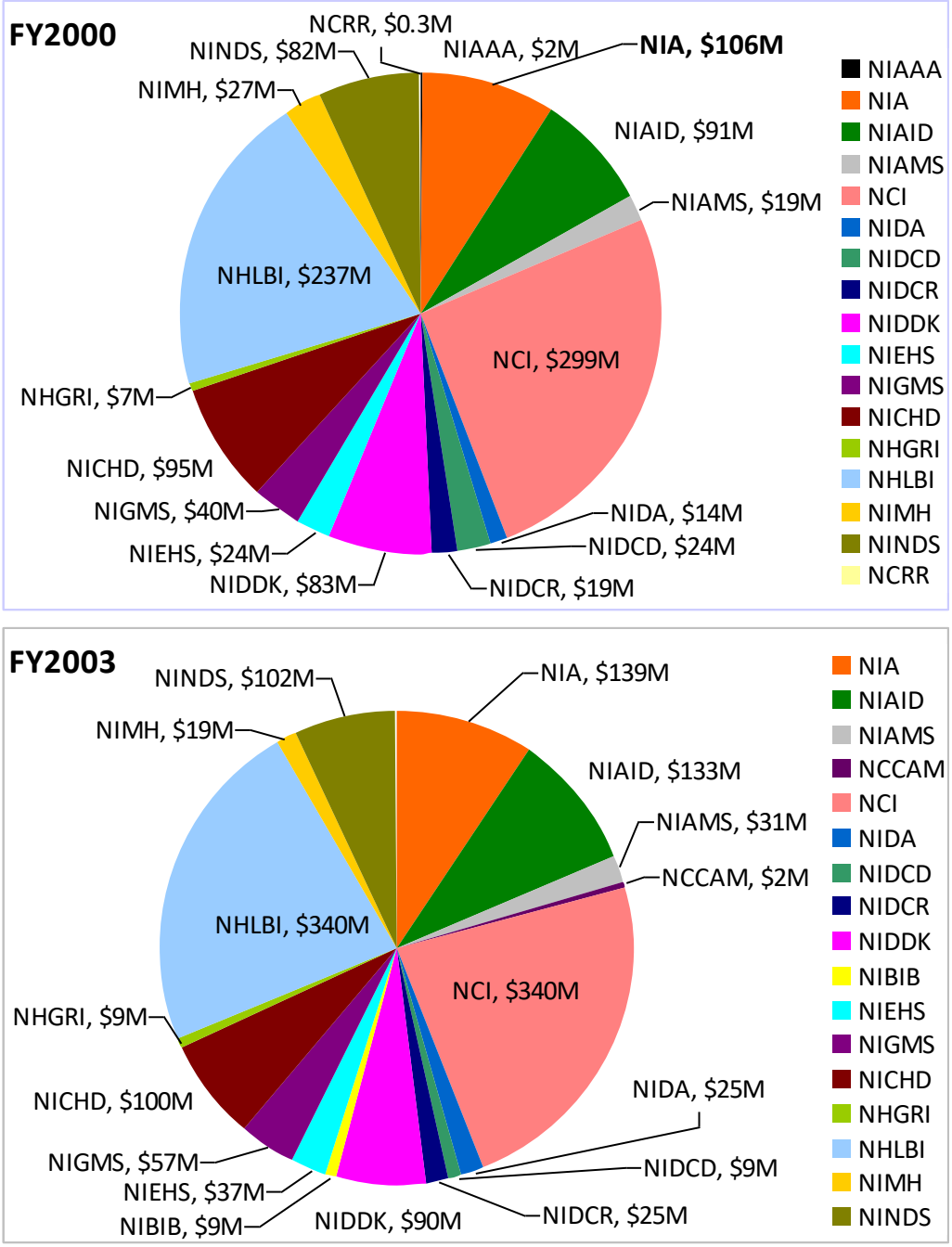
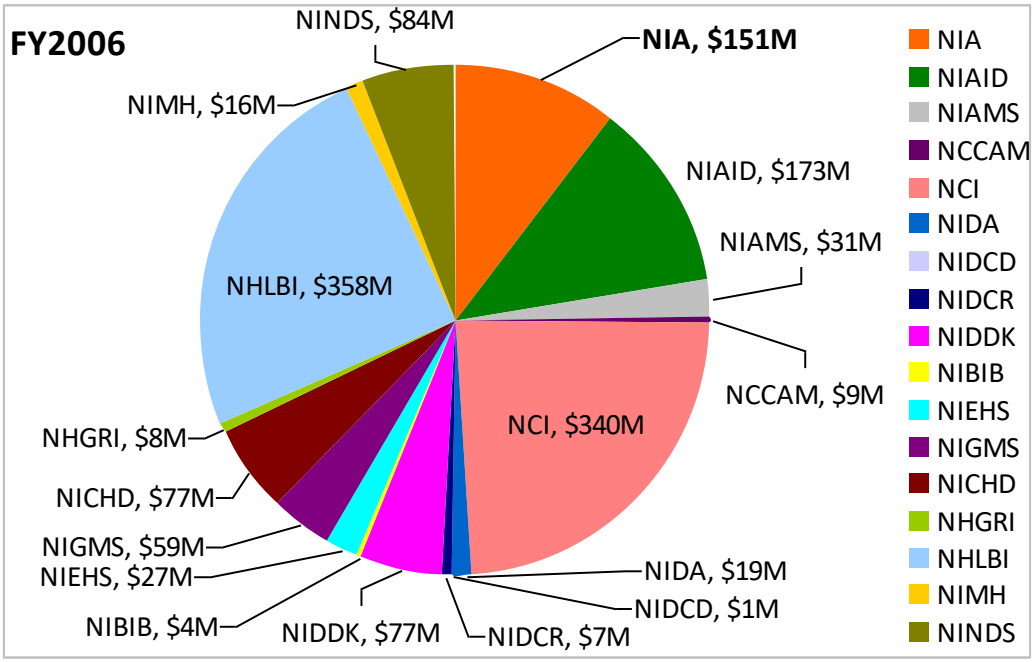
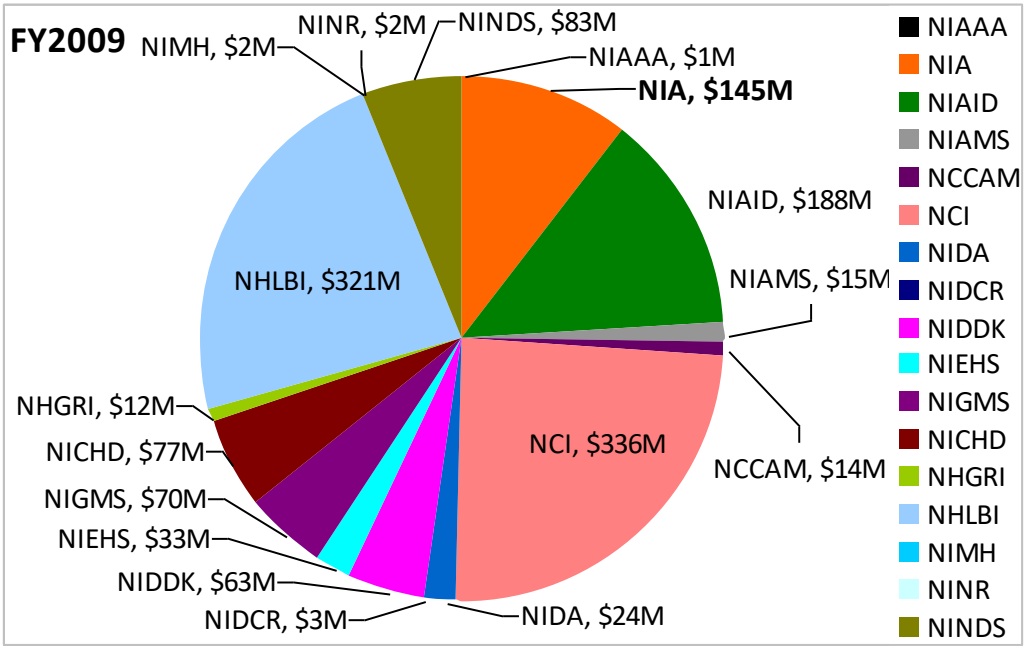


Exhibit 7: P01 Total Costs by Institute and Center for Selected Years





Data Source: QVR
ICs with no P01s in FY2000: NCCAM, NIBIB, NINR
ICs with no P01s in FY2003: NINR
ICs with no P01s in FY2006: NIAAA, NINR, NCRR
ICs with no P01s in FY2009: NIDCD, NIBIB, NCRR
ICs with no P01s in any of the years: NEI, NLM, NCMHD, FIC

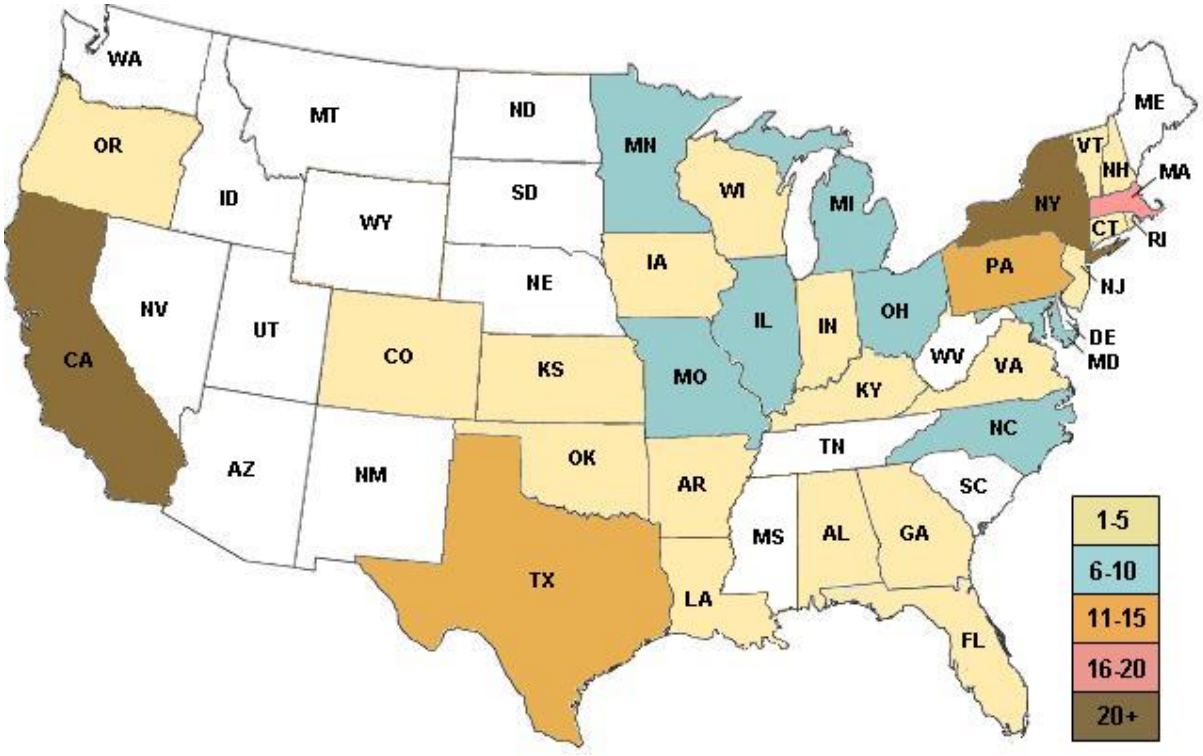
Exhibit 8: Numbers of P01 grants by Institute and Center for Selected Years

	FY2000	FY2003	FY2006	FY2009
NCI	211	265	179	169
NHLBI	160	219	179	156
NIAID	109	168	108	100
NIA	88	118	96	89
NINDS	87	102	67	67
NIDDK	79	90	59	44
NICHD	61	97	56	57
NIGMS	42	57	41	40
NIEHS	27	41	22	26
NIDCD	26	18	1	0
NIDCR	25	26	6	2
NIMH	20	18	10	1
NIAMS	19	31	24	11
NIDA	17	26	17	19
NHGRI	4	0	1	3
NIAAA	1	1	0	3
NCRR	1	1	0	0
NINR	0	0	0	3
NIBIB	0	7	3	0
NCCAM	0	16	8	11

Institutes with no P01s in FY2000, 2003, 2006, and 2009: NEI, NLM, NCMHD, FIC

Exhibit 9 illustrates the distribution of the 210 NIA-supported P01 grants included in this evaluation by state. The top three states were California (37 grants), New York (36 grants), and Massachusetts (20 grants).

Exhibit 9: NIA P01s by Number of Renewals, FY1990-2010



Data Source: QVR

The Role of P01s in Promoting Interdisciplinary Science

NIA scientific staff identified the promotion and fostering of interdisciplinary research as one of the primary benefits that they hope to gain through the program project grant (P01) mechanism. They have found the P01 useful for integrating interrelated studies around a common research theme and for allowing principal investigators with expertise and backgrounds in multiple scientific disciplines and fields to work together on challenging multifaceted research questions. For example, the investigator team involved with P01-AG-26571, "Behavior on Surveys and the Economy Using HRS," a study on decision-making and well-being using data from the Health and Retirement Study led by Robert Willis of the University of Michigan, includes both economists and psychologists.[1] The study funded through P01-AG-11915, "Dietary Restriction and Aging in Rhesus Monkeys," is another example of multidisciplinary research with basic and clinical components including brain imaging. The grant is supported jointly by the Division of Aging Biology and the Division of Neuroscience.

[1] This team also receives support from the private sector and RAND Corporation.

NIA program staff provided the following additional examples of how P01 grants have promoted interdisciplinary research:

- P01-AG-14449, "Neurobiology of Mild Cognitive Impairment in the Elderly." This study relies on a network of collaborations bringing together basic and clinical scientists from the Chicago area and outside universities to collect samples and data on cognitive testing and publish results of the longitudinal clinicopathological studies of aging and dementia. The research conducted through this P01 relies on investigators from these laboratories obtaining samples and clinical data from the Religious Orders Study. The P01 allows for these multiple efforts and sites to collaborate under one mechanism.

- P01-AG-29409, "Economics Status, Health, & Well-Being over the Life Course and Across Generations." Also called the Panel Study of Income Dynamics (PSID), this research project is the world's longest running household panel study spanning more than four decades [beginning in 1968]. The research involves economists, health policy analysts, statisticians, software engineers, physicians, epidemiologists, social scientists, and psychologists, among others.

- P01-AG-26276, "Antecedent Biomarkers for AD: The Adult Children Study." This grant supports projects to study amyloid imaging, performance profiles, anatomical biomarkers of AD, and amyloid beta metabolism. The researchers are currently looking at changes in markers in cerebrospinal fluid. Co-investigators include neuroscientists, clinicians, and radiologists, among others.

- P01-AG-18911, "Social Isolation, Loneliness, Health, and the Aging Process." This grant brings together sociological, psychological, and biological levels of analyses to examine the relationships among and mechanisms underlying social isolation, feelings of loneliness, health, and the aging process. It reflects both a broad and sweeping style of integration of human laboratory, epidemiological, and animal approaches to social relations and health and more specific and highly persuasive instances of integration.

- P01-AG-003991, "Healthy Aging and Senile Dementia." Led by John Morris, this grant facilitates interactions among neuroscientists and clinicians to help diagnose the early stages of AD sooner and more accurately by measuring biomarkers—tau and beta-amyloid proteins—in cerebrospinal fluid. Publications in a variety of journals including JAMA, Neurology, Biological Psychiatry, and Nature Genetics are evidence of the interdisciplinary integration of the various types of expertise involved.

- P01-AG-026423, "Evolution of Aging and Dementia in Female Primates." Led by James Herndon, researchers from various disciplines who have not worked with chimps before are now comparing human brains and cognitive aging with the same features in chimpanzees and in the most widely studied biomedical model of human aging, the rhesus monkey.

- P01-AG-009973, "Cognition and Hippocampal/Cortical Systems in Aging." Led by Michela Gallagher at Hopkins, this team is pursuing a multidisciplinary, integrated approach using rodent models to understand the effects of normal aging in brain systems that support cognitive functions affected in humans as they age. This research brings together investigators with different expertise from UC Davis, Mt. Sinai, and Stony Brook to study how interventions based on the study of neurocognitive aging in the rodent brain could potentially be effective in non-human primates.

- P01-AG-026571, "Behaviors on Surveys and in the Economy: HRS and Beyond." Robert Willis leads a cross-disciplinary economics/psychology team that includes members from the private sector as well as several investigators from across institutions and disciplines. They are involved in a study of the concepts and methods of modern economics as it relates to the traditional problem of well-being in psychology, and the insights of modern psychology about well-being on the problems in economics of prediction of behavior, understanding expectation formation, and welfare analysis.

- P01-AG-031093, "Networks and Neighborhoods." The Nicholas Christakis team combines medical and political science and analyzes important aspects of clinical care, basic social science, and health policy.

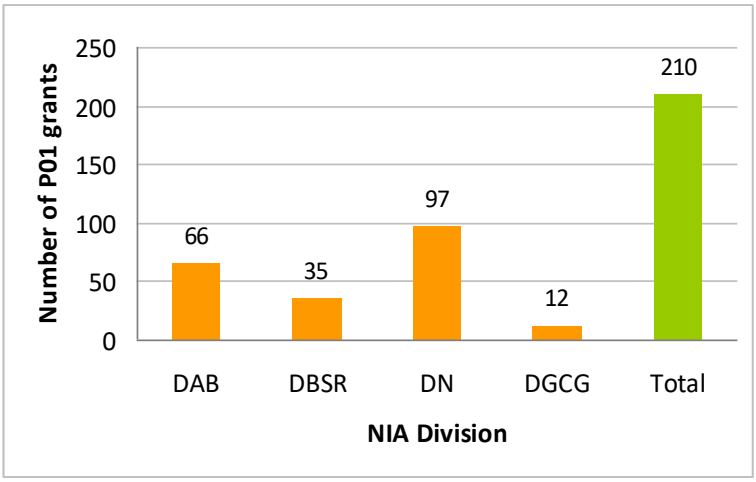
Some P01s involve research in multiple institutions, some only one. Vincent Mor started his P01 on shaping long-term care in America as a long-term care specialist at Brown University. Then, with his P01, he branched out to Harvard and Dartmouth, creating an unofficial consortium among the Northeastern universities. Investigators at Dartmouth are now doing research on Medicare and researchers at Brown are looking at aging research and long-term care. None of these investigators were previously working in aging research, but their research now focuses on aging and long-term care.

Some Centers programs provide a common research theme and interdisciplinary approach similar to the P01 mechanism. The Alzheimer's Disease Centers (ADC) program, for example, funds 30 Centers that include areas of investigation ranging from the basic mechanisms of AD to managing disease symptoms and helping families cope with the effects of the disease. Center investigators cover the full medical research continuum from basic scientists to clinical researchers. Investigators conduct research in areas of behavioral and social science, neuroscience, psychology, and immunology, among others.

A Request for Applications can also facilitate interdisciplinary research by soliciting applications from a variety of disciplines around a common theme as demonstrated with the Genetic and Molecular Basis of Longevity ("LAG") RFA. The network was conceived to promote a multidisciplinary approach with several grantees working in parallel on similar problems using different animal models. For example, investigators with R01-AG-24354 and R01-AG-24366 examined the relationship between caloric restriction and longevity in mice and in Drosophila, and investigators on grants R01-AG-11659 and R01-AG-11687 used genetic tools in worms and mice to identify genes that contribute to longevity.

Exhibit 10 shows the distribution of the 210 P01 grants included in this evaluation by NIA division based on their total costs, which were obtained from QVR. During the timeframe examined, the Division of Neuroscience funded 100 P01s, and the Division of Aging Biology funded 67 P01s. Four of the grants were co-funded by two or three divisions, and these grants are included in the column for the lead division.

Exhibit 10: Number of P01 Grants by NIA Division, FY1990-2009

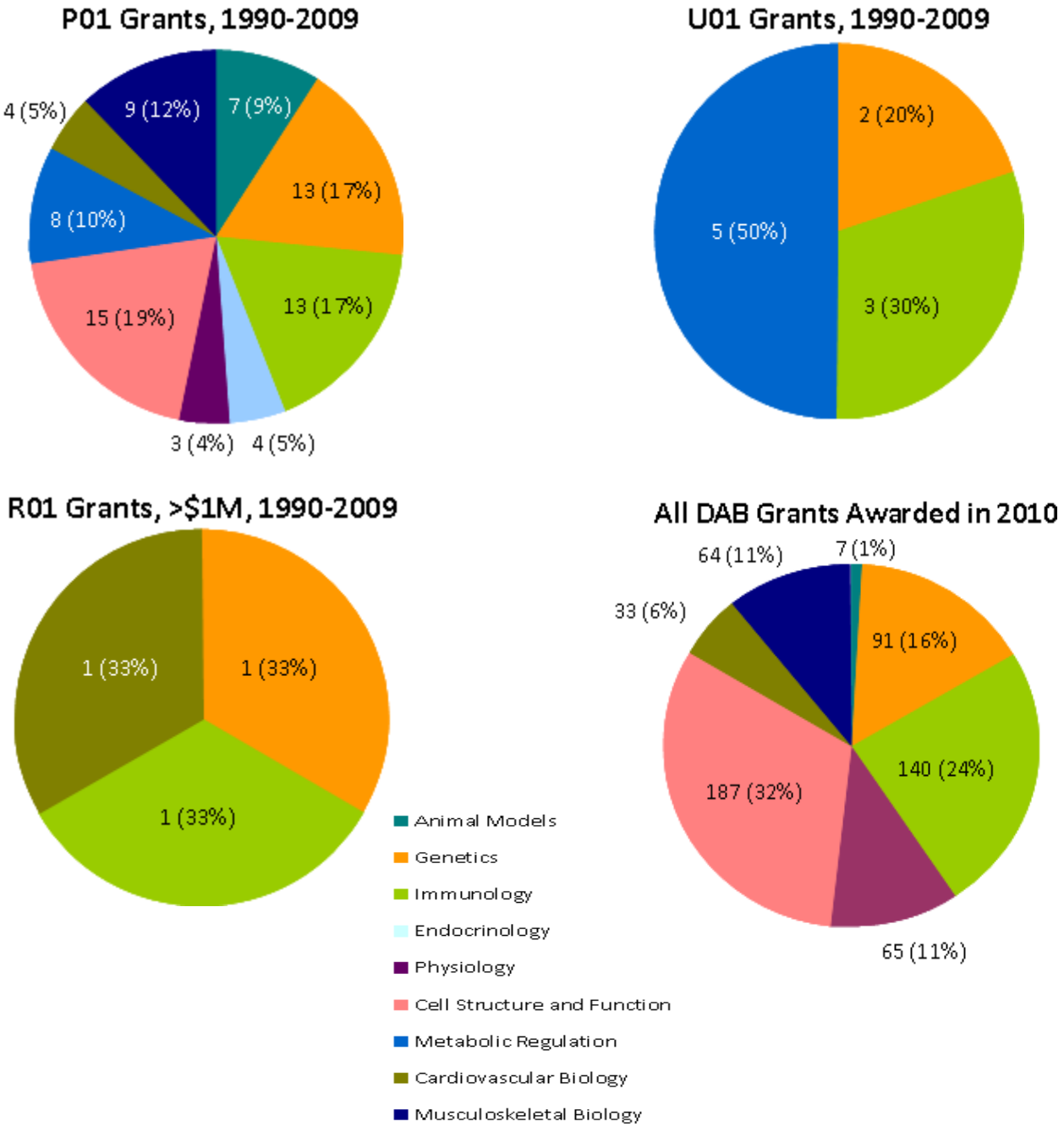


Data source: QVR
Grants co-funded by more than one division:
P01AG017553 (DN, DAB, DBSR)
P01AG025901 (DN, DAB)
P01AG012993 (DN, DAB)
P01AG027735 (DGCG, DBCR)

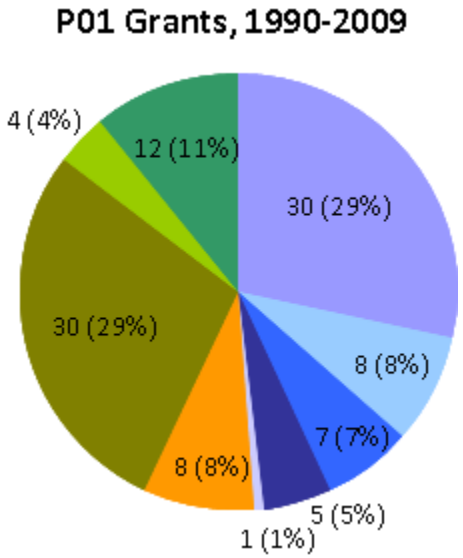
For Exhibit 11, each P01, U01, and large R01 from 1990-2009 was categorized by NIA division's scientific topic areas as provided on the NIA public website. For some projects, the grants were relevant to more than one area. Thus, some projects were counted more than once for a specific division, making the total numbers in these charts sometimes exceed the total numbers of unique grants included in this evaluation and shown in Exhibit 10 (for P01s). For example, 66 grants were funded by DAB (Exhibit 10), but several of these were assigned to more than one scientific topic area within DAB and in some cases to another NIA division. Therefore, the count of grants for DAB in Exhibit 11 adds up to 76.

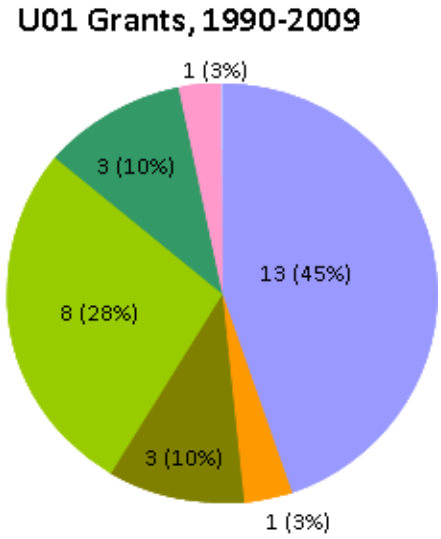
Exhibit 11: Distribution of P01, large R01, and U01 grants by Research Area - Percentage and Number by Research Area for Each NIA Division

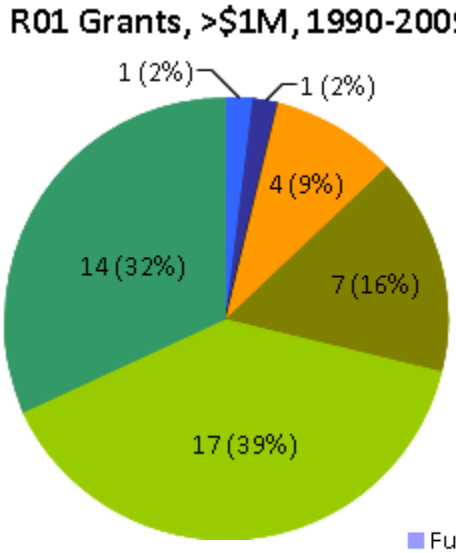
A. Division of Aging Biology

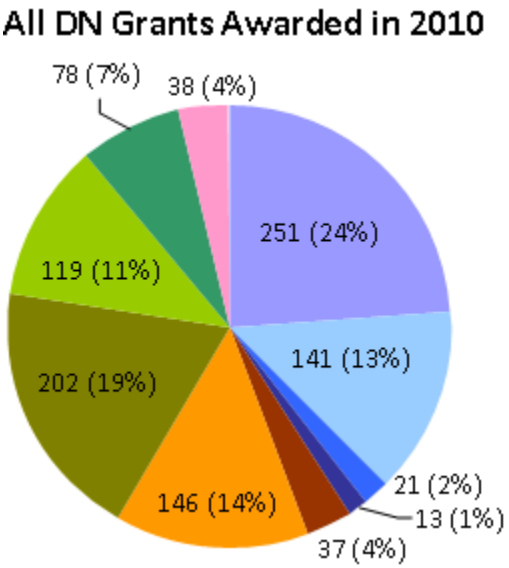


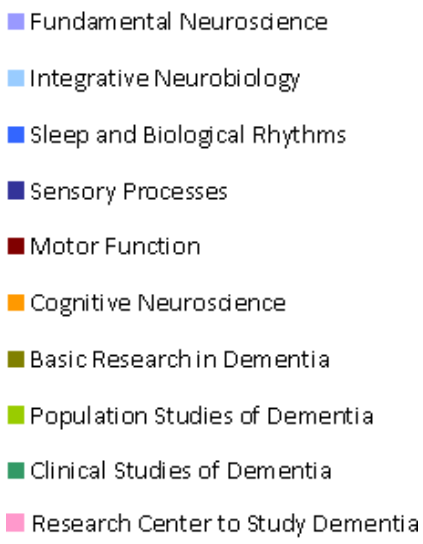
B. Division of Neuroscience



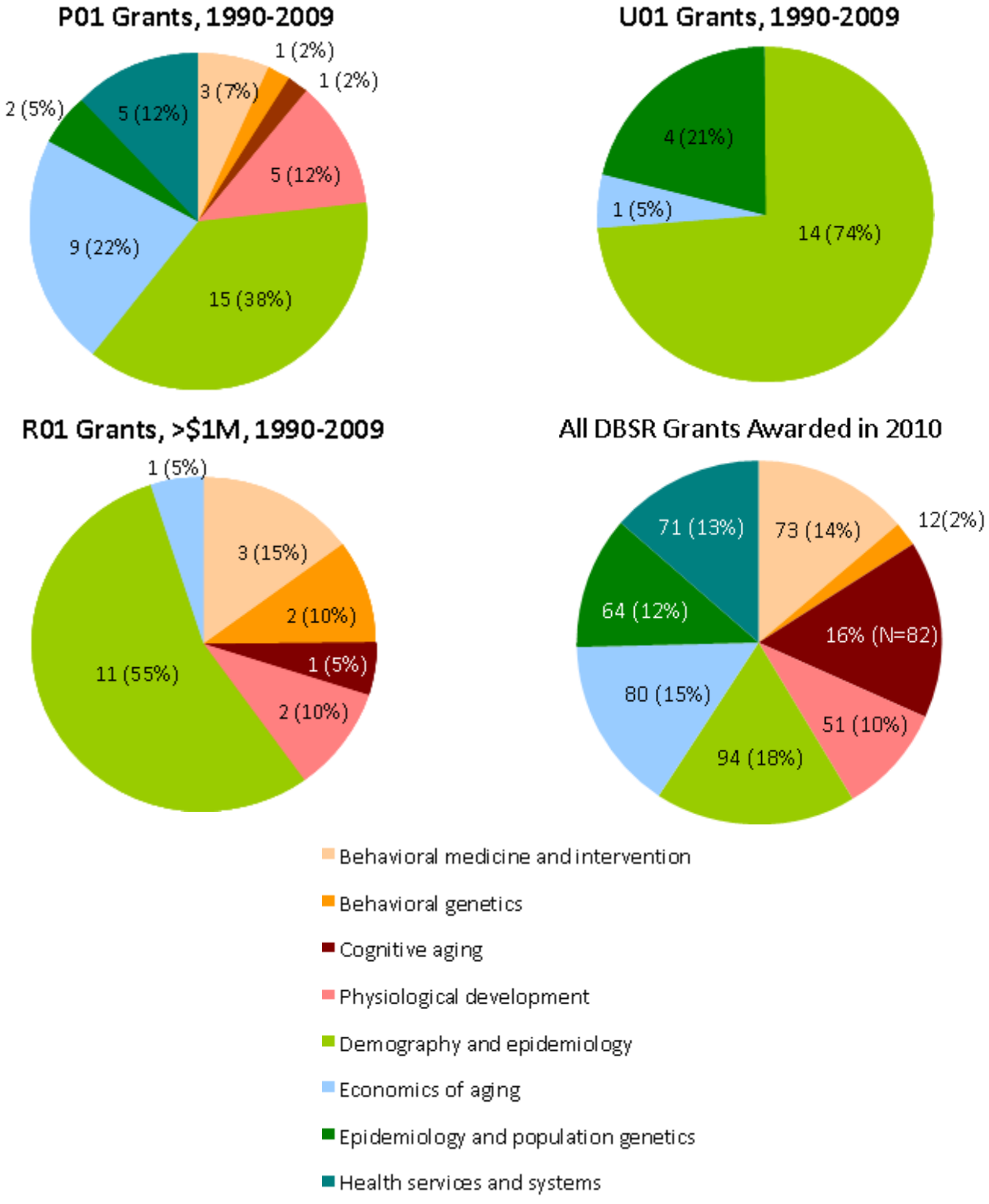




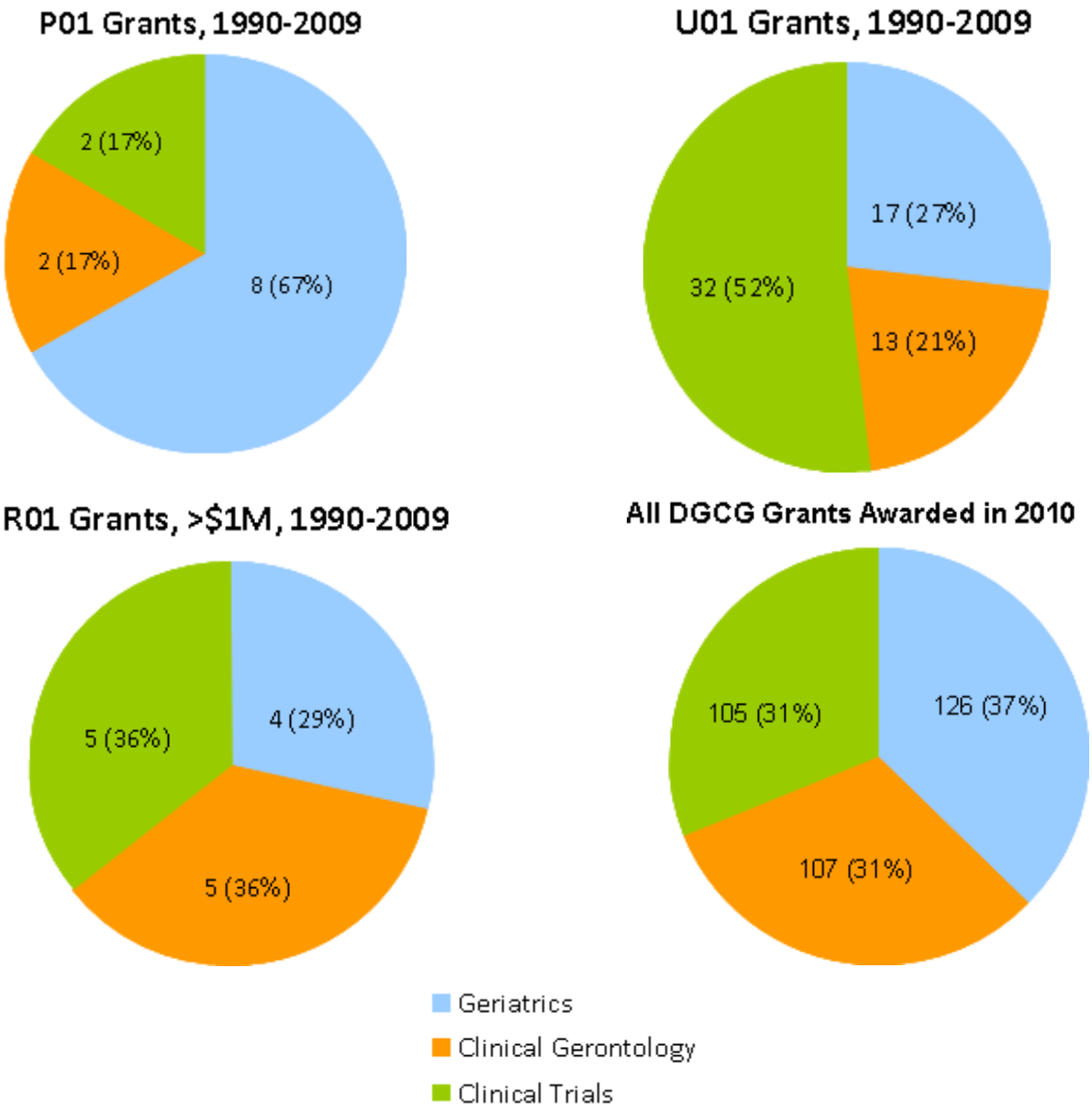




C. Division of Behavioral and Social Research



D. Division of Geriatrics and Clinical Gerontology



Source: QVR

The Role of P01s in Facilitating High Quality Research

While pointing out that any funding mechanism can facilitate high quality research, NIA staff members cited the examples below of significant scientific outcomes that have resulted from investments in P01s. Additional examples are included in other parts of this report.

P01-AG-17586, "Frontotemporal Dementias: Genotypes and Phenotypes." This research has led to novel discoveries and has been instrumental for some of the GWAS studies that point to new ways of thinking about frontotemporal dementias. Investigators obtain both post mortem and anti-mortem

samples from the cohort under study and these have been used for making models of some of the biopathways studied.

Several studies on Alzheimer's disease:

- P01-AG-25204, "In Vivo PIB PET Amyloid Imaging" and P01-AG-09464, "Signaling Transduction and Alzheimer's Disease," which have allowed for new discoveries in animal and cell models, PET imaging and PIB, and tau and APP processing.
- P01-AG-25831, "Amyloid Plaque and Tangle Imaging in Aging and Dementia," and P01-AG-26276, "Antecedent Biomarkers for AD: The Adult Children Study," which have focused on mechanisms that drive amyloid deposition in Alzheimer's with particular attention paid to effective early diagnosis and differential diagnosis of dementia and age-related memory loss, providing the basis for reliable methods of testing interventions designed to delay the onset of dementia and treat it once it develops, and for identifying the earliest brain changes of AD, determining the evolution of these changes over time, and assessing their predictive power for the eventual development of symptomatic AD, respectively.
- P01-AG-26571, "Behavior on Surveys and in the Economy using HRS," and P01-AG-05842, "Economics of Aging." These studies, led by Robert Willis and David Wise, respectively, involve innovative research to test economic theories bringing together expertise on aging, economics, and psychology. The Willis team is applying the concepts and methods of modern economics to the traditional question of well-being in psychology and the insights of modern psychology about well-being to traditional questions in economics related to the prediction of behavior. The Wise team is pursuing an analysis of the psychological determinants of economic decision-making, particularly the influences on retirement saving decisions. Findings from this research have led to legislative changes related to 401Ks.
- P01-AG-29409, "Economics Status, Health, & Well-Being over the Life Course and Across Generations." This study has contributed to new sampling and data collection methodologies for use in large population-based surveys and behavioral interventions as well as to new analytical approaches to data. The long panel, genealogical design, and broad content of the study represent a unique opportunity for a multi-perspective study of life course evolution and change within families over three generations.

One indicator of the quality of the research might be number and cost of publications. Exhibit 12 shows the total number of publications per grant mechanism, the average number of publications per grant, and the cost of publication per grant dollar. P01s had the highest publication total and the highest average number of publications per grant. Because P01s had the highest total expenditures and total number of publications across the grant mechanisms, the cost per publication for P01s was lower than for comparison mechanisms.

Exhibit 12: Cost of Publication for P01, Large R01 and U01 Grants

	P01s	Large R01s ($1M+/yr)	U01s
Total Number of Projects	210	81	120
Total Number of Publications*	12,902	1,908	1,928
Total Costs	$1,988,995,344	$453,557,877	$953,493,374
Average Number of Publications per Grant	61	24	16
Cost per Publication**	**$154,162**	**$237,714**	**$494,551**

Data source: eSPA and QVR

*Publication counts include only research articles; no self-citations as defined by eSPA: Those articles for which the citing and the cited paper have at least one author in common are flagged in the eSPA back-end databases. By default, articles for which any author matches a Project PI *and* all articles related to it by self-citations are excluded from the publication list. Users can choose to include self-citations in their publications results by checking the "Include Self-Citations" box.

**Total Costs divided by Total Number of Publications

In a given year, the impact factor of a journal is the average number of citations received per paper published in that journal during the two preceding years. Exhibit 13 suggests that P01s have almost 3 times as large an **impact factor per grant** than the other mechanisms examined. Publications resulting from P01 projects in this evaluation had slightly higher **impact factor per publications** than either large R01 or U01s. **Cost per impact factor** was lower for P01s compared to either large R01s or U01s.

eSPA was used to generate data for the research publications and impact factors. The projects included in this calculation were randomly selected and include the publications for 48 P01s, 12 large R01s, and 22 U01s. Project count, numbers of publishing projects, and total cost data were calculated using QVR. The calculation of average impact factor per publication and per grant represents the total impact factor divided by the quantity of publications and by the number of grants, respectively. The total cost per impact factor was generated by dividing the total cost of the randomly selected grants by the corresponding total impact factor.

Exhibit 13. Cost Per Impact Factor by Grant Mechanism

	P01s	Large R01s ($1M+/yr)	U01s
Sum of Impact factor*	10,629	916	1,857
Total Number of Publications**	2,422	233	470
Average Impact Factor/Publication	**4.38**	**3.9**	**3.95**
Number of Grants	48	12	22
Average Impact Factor/Grant	**221.4**	**76.3**	**84.4**
Total expenditures	$308,346,319	$47,018,009	$109,957,905
Cost/Total Impact Factor	**$29,009.90**	**$51,329.70**	**$59,212.65**

Data source: eSPA and QVR

* We were unable to download from eSPA all of the publications for the 210 P01s included in this evaluation, thus 48 projects were selected at random. A comparable number of large R01s and U01s were randomly selected.

** eSPA uses the ISI Web of Science definition of Impact Factor. Impact Factor is a journal-based indicator that is calculated based on the historical average citation rate for articles in a given journal and provides an estimate of the number of expected citations for an article within the first 2 years following publication. The indicator is recalculated on a bi-annual basis; for example, articles published in *Cell* in 1998 will have a different impact factor than articles published in *Cell* in 2006. This information is captured from the ISI Web of Science Select database and is updated in eSPA on an annual basis. These data are available from 1994 to present.

In a given year, the impact factor of a journal is the average number of citations received per paper published in that journal during the two preceding years.

*** Research publications only; no self-citations as defined by eSPA.

The Role of P01s in Initiative New Areas of Research

The NIA Program Officers who we interviewed cited P01 grants as powerful tools that have jumpstarted research in specific topic areas to address scientific and health research challenges in both biomedical and behavioral research:

- P01-AG-22500, "The Biodemography of Life Span." A geneticist taking a population perspective, James Carey and his team have initiated innovative studies using animal models for biodemography, and have established a new direction involving the testing of revolutionary hypotheses using wild animals in research. Biodemography is the study of complementary biological and demographic determinants of and interactions between birth and death processes that shape individuals, cohorts, and populations.

- P01-AG-8761, "Oldest-old Mortality - Demographic Models and Analysis." Investigators have started examining male and female differences in mortality through cross-species comparative work that no one investigator can study. Their research includes baboons, Americans, South Asians, and is testing a common hypothesis across species and human populations.

- P01-AG-00538, “Behavioral and Neural Plasticity in the Aged.” This research was first funded in 1977. In 2001 and 2002, research into amyloid beta was an emerging field that was jumpstarted through the discovery in the early 1990’s that the protease inhibitor protease nexin-II (PN-2) is the secreted form of the amyloid beta-protein precursor containing the Kunitz inhibitory domain. Testing the hypothesis that amyloid beta is one of the major contributing factors to the development of AD continues through the P01 mechanism and now is also extensively studied through Centers, R01s, and other mechanisms. This area of research has greatly expanded over the years and now includes AD imaging with two different ligands allowing researchers for the first time to study the living brain and identify brain changes.

- P01-AG-19783, “Causes and Consequences of Health Care Intensity” (Newhouse) and P01-AG-32952, “The Role of Private Plans in Medicare” (Skinner). A component of the recently enacted health care reform law to greatly expand insurance coverage without a negative budget impact was strongly influenced by research conducted through these P01s. The Joe Newhouse study focused on Medicare Advantage and the Jon Skinner study focused on geographic variation measures. These two projects helped to form the centerpiece of the health care reform legislation and jumpstarted research on the relationship between health care spending and better health outcomes.

- P01-AG-20166, “Integrative Pathways to Health and Illness.” This project includes the National Survey of Midlife Development in the United States (MIDUS), which has been significantly enhanced through the P01 mechanism. Originally funded by the McArthur Foundation, funding through the P01 mechanism now allows for more assessments and multilevel samples of well-being, emotional health, stress, cognitive health, and cortisol measures, among other measures and assessments.

- P01-AG-26423, “Evolution of Aging and Dementia in Female Primates.” This project will for the first time evaluate and compare cognitive, emotional, brain structure and function, and biomarker data in aging humans, rhesus monkeys, and chimpanzees. Novel and important insights into human brain aging can be obtained by these comparative studies. This comparative approach is unique to the P01 and could not be accomplished through other mechanisms.

- P01-AG-27296, “Shaping Long-term Care in America.” Through this P01, the Long-Term Care Minimum Data Set (MDS) is being used to measure health outcomes relating to physical, psychological and psychosocial functioning. This data gives a multidimensional view of a patient's functional capacities and provides a summary outcome measure and an indicator of health status. The Schoeni P01-AG-29409, “Economics Status, Health, & Well-Being over the Life Course and Across Generation” is another example of data being used for analysis of medical fee-for-service claims. These P01s have opened up awareness that these data resources can be used for analyses and applications are now written using these data and are being treated seriously in study sections.

- P01-AG-04875, “Physiology of Bone Metabolism in an Aging Population.” P01s have jumpstarted testosterone deficiency and DHEA research at the Mayo Clinic. An original R01 funding of bone changes related to estrogen and its effect on multiple tissues, fat, glucose, etc., was later awarded as a P01 to further the science studied and coordinate efforts across the disciplines, including exercise-induced biochemical and anatomical adaptations both in animal and clinical setting. This coordinated approach would not have been possible with small R01s and R21s.

RFAs can also be used to jumpstart a new or emerging area of research. Neuroeconomics is one area that has been galvanized through an RFA. The RFA to stimulate drug discovery for Alzheimer's disease, which was issued at a time when very little research was being conducted in academia, is another good example. Issuance of this RFA resulted in an increase in research in this area and later five or six P01s were awarded, two of which are still ongoing and have taken drug compounds into trials. Research funded through the Genetic and Molecular Basis of Longevity ("LAG") RFA initiative contributed to expansion of the emerging field of the genetics of aging. In particular, the use of lower eukaryotes – yeast, fly, and worm – helped identify new genes affecting the aging process. Findings of aging determinants from these model systems were then extended to mice and humans.

The Role of P01s in Providing Infrastructure to Support Large, Complex Research Projects

There are Program Project Grants that NIA has funded for 10, 15, or more years. Program Project Grants are required to have at least one core, often an administrative core, but these grants usually establish other cores such as cores for animal models, chemicals, bioinformatics, and statistical analyses. Cores or similar resources may also be available to principal investigators through other programs at their research institution. Examples of P01 infrastructure cited by NIA scientific program staff include:

- P01-AG-03991, "Healthy Aging and Senile Dementia." Funded for more than 20 years, the P01 infrastructure has allowed Dr. John Morris to study the trajectories of disease through the transitional phase of MCI and measure psychological aspects, cerebrospinal fluid, and imaging. Through the neuropathology, neuroimaging and clinical cores, early data can be reviewed and researchers can determine the earliest indicators of disease, see what happens over time, and identify at what point decline begins.

- P01-AG-07996, "Studies of Joint Aging and Osteoarthritis." This study includes a Morphology Core that procures knee joints, a critical resource for the project that has allowed investigators to analyze the role of articular aging in the pathogenesis of osteoarthritis and make comparisons that would otherwise have been very expensive if carried out separately.

- The Panel Study of Income Dynamics (PSID) is a large complex research project that is supported by a P01 infrastructure for collecting dynamic aspects of economic and demographic behavior, with broad content including sociological and psychological measures. This is accomplished through NIA, NSF and NICHD co-funding.

- P01s provide a needed infrastructure particularly when research is built around a data set such as the Medicare or health insurance data. Through the P01 mechanism, there is an economy of scale and support for large data collection as well data sharing through the cores.

- P01s formalize collaborations. The "IGF-1 in the AMES Dwarf Mouse" P01 has involved several IC collaborations, which are far less likely to occur without a P01 infrastructure.

Program officers have pointed to resource sharing and looking across systems as a cost efficient way of performing research. For example, P01s have been especially successful in research involving high-throughput technology, and cores have been established that support PIs with limited expertise in computational or statistical research and help investigators work better together.

Some of our interviewees believe that, depending on the nature of the science involved, the cost of P01 funding for longitudinal studies may not provide NIA with the best value. Some divisions use the U01 mechanism for these types of studies because there is less benefit in using P01s. In terms of

recruitment, standardization, and training, there seems not to be agreement about whether the P01 mechanism is better than an R01 or a U01.

Some Centers programs also provide the capacity for promoting multidisciplinary integration and resource sharing, as well as career development. NIH requires all 30 Alzheimer's Disease Centers to have the following cores: administrative, clinical, data management and statistics, education and information transfer, and neuropathology. Some centers include other optional cores such as Neuroimaging or genetics cores, and some have satellite diagnostic and treatment clinics to help recruit minority or rural research participants.

The Role of P01s in Moving Science along the Translational Continuum

A number of mechanisms promote translational science and the bench-to-bedside approach. P01s are well suited for moving science along this continuum because of their interdisciplinary nature. P01 studies of the characteristic amyloid plaques found in the brains of Alzheimer's patients have moved forward to the point that scientists are now carrying out preliminary tests in humans of potential therapies aimed at removing beta-amyloid, halting its formation, or breaking down early forms before they can become harmful. An example of early work in amyloid beta is P01-AG-00538, "Behavior and Neural Plasticity in the Aged". The development, within the past decade, of reliable transgenic animal models that closely replicate the pathology, symptoms, and disease course of AD has also accelerated the pace of progress in this area through a P01 grant: P01-AG-009973, "Cognition and Hippocampal/Cortical Systems in Aging". The calorie restriction (CR) in humans grant, P01-AG-034907, "Does Calorie Restriction Slow Aging in Humans?" is another example of success in translational science, with the comparative study of CR and exercise and the use of novel approaches for translating knowledge about animal pathways into studies in humans.

Other cited examples of translational research through P01s include:

- Five P01s resulting from PAS-AG-05-022, "Grants for Alzheimer's Disease Drug Discovery," two of which successfully advanced drug compounds into clinical trials. The P01s have allowed researchers to translate basic science findings into clinical trials to evaluate treatment and prevention strategies. This research has led to the discovery, development, and preclinical testing in cellular, tissue, and animal models of novel compounds for the prevention and treatment of the cognitive impairment and behavioral symptoms associated with AD.

- The "Experience Corps Trial" under P01-AG-27735. This trial has served as a means of evaluating the effectiveness of a major community intervention designed to improve social, cognitive, and physical functioning among poor, inner-city elderly. Experience Corps recruits older people for cognitively challenging, meaningful roles as volunteers in inner-city elementary schools. The program is active in 19 cities nationwide. The evaluation is a double-randomized treatment-comparison group study of effects on both the older volunteers and on the school children in Baltimore.

- P01-AG-27734, "Role of Genes in Exceptional Longevity in Humans." Dr. Nir Barzilai's research team is working to understand the role that cellular proteins play in preventing nerve cells from dying and helping to improve insulin action and lowering blood glucose levels. These proteins protect nerve cells from death associated with Alzheimer's and other brain diseases and have potential to be a therapeutic option for age-related diseases.

- P01-AG-10435-17A2, “Gene Therapy for Alzheimer's Disease.” Researchers are exploring the influences of genes and the environment on neuronal vulnerability to degeneration in aging and AD, thereby identifying potential translational therapies for humans with AD.

- P01-AG-17490, “Cellular Co-factors, Neuronal Stress, Aging and AD.” This research includes examination of abnormal aggregation of proteins in neurodegenerative diseases; protein interactions such as presenilin-binding proteins; and the interactions between amyloid-beta peptide and apolipoprotein E in AD. Researchers have moved from looking at the amyloid hypothesis to different ways that amyloid might affect neuron metabolism and are now looking at mitochondria at the synapse in the context of AD and how pharmacologic compounds might have an effect on this.

We found that there are different perspectives about whether P01s are more advantageous for basic versus clinical research. There was a great deal of agreement that the potential for P01s to help foster interactions among researchers may make them a good option for supporting translational work.

Our interviewees also indicated that some Center programs may be equally as valuable for promoting translational science. The Edward R. Roybal Centers for Research on Applied Gerontology, for example, seek to move promising social and behavioral research findings out of the laboratory and into programs and practices that will improve the lives of older people and help society adapt to an aging population. The Centers focus on a range of projects including maintaining mobility and physical function, enhancing driving performance, understanding financial and medical decision making, and sharpening cognitive function. Although each Center focuses on a particular aspect of aging, all of the Centers concentrate on the translation of research into applications that can be moved quickly into practice. In addition, the ADCs are working to translate research advances into improved diagnosis and care for AD patients in support of the program’s long-term goal of finding a way to cure and possibly prevent AD. Translational efforts are bolstered through the collaborative efforts and shared resources with other research programs such as the AD Cooperative Study and the AD Neuroimaging Initiative.

The Role of P01s in Attracting Top Researchers to Aging Research

Some of the program staff members we interviewed believe that one of the greatest advantages of the program project grant is project leadership by an experienced investigator. This leader is able to put together a group of scientists with complementary abilities and backgrounds, disciplines, and perspectives. Through these integrated, synergistic efforts, the program project grant can be quite a powerful mechanism, attracting top researchers to collaborate and enjoy the benefits of a multidisciplinary setting. However, not all staff agree that this synergy and coordinated effort across a common research theme necessarily occurs in every P01 project. Some believe that research conducted within some P01s is very similar to that in many R01s where each investigator works on a specific area of study that may not be relevant to the work of other investigators supported by the same grant.

Staff members say that program project grants are rarely awarded to young or junior investigators primarily because of the complexity of preparing a P01 application which requires the skill of an experienced scientist. Younger investigators are incorporated into the P01 so they can work with experienced scientists. A number of young investigators do receive funding for their first projects through a subproject of a P01, and there is evidence that young scientists are brought into the field of aging research and given a jumpstart to conduct their research by being part of a P01. As co-investigators, they ride the coattails of the senior PIs who are leading the P01s. Certain P01s are also led by a relatively junior PI in collaboration with more senior PIs. These projects sometimes score well

because of the reputation of the senior PIs involved, but may at other times not score well because of the inexperienced junior investigator.

There are numerous examples of individuals whose work is not specifically focused on aging who are bringing their expertise to the field. They include scientists specializing in genetics, neuropsychology, cognitive behavior, pharmacology, and anatomy, among others. Staff members cited some examples of situations where P01s have attracted top researchers to the field of aging research.

- Vincent Mor started his P01-AG-27296, "Shaping Long-Term Care in America," as a long-term care specialist at Brown University. Then, he branched out to Harvard and Dartmouth, creating an unofficial consortium among northeastern universities. Investigators at Dartmouth are now doing research on Medicare and researchers at Brown are conducting aging research and long-term care. None of these investigators were previously working in aging research, but their research now focuses on aging and long-term care.

- Michela Gallagher, P01-AG-9973, "Cognition and Hippocampal/Cortical Systems in Aging," had a project that was led by Peter Rapp, an early investigator who became a leading researcher at Mt. Sinai. Rapp then left Mt. Sinai and joined NIA as a lab chief.

- Susan McLennon worked on the Wise P01-AG-27296, "Shaping Long-Term Care in America," and later became an Administrator at CMS. The Arie Kapteyn P01-AG-22481, "Economic and Health Determinants of Retirement Behavior" included a physicist - not a typical discipline for aging research - who recently received the Marshall Scholar award as a prominent young investigator.

The Role of P01s in Building Relationships for Future Collaboration

Our interviewees believe that using the P01 mechanism in situations where the need is to examine the same research area from different perspectives is a real advantage. Experienced investigators are able to put together groups of scientists with complementary abilities and experiences to analyze a given area of science. P01s do not necessarily lead to better communication, but do tend to be more interactive and build synergy and relationships that endure over long periods of time.

Examples cited to illustrate collaborations and relationship-building around P01s include:

- P01 connections that persist beyond the P01 lifetime as co-investigators continue working through separate R01s.

- Center pilot projects that continue to build under the auspices of a P01.

- Studies involving partnerships with other ICs – for example, the studies of life course, trajectories, and health and well-being supported through a partnership with NICHD.

- A P01 with a focus on genetic information and social architecture that led to a PAR/RFA.

- Synergy around P01-supported Amyloid beta (Aβ) research that is now considered to be one of the major contributing factors to the development of AD research.

- Meetings coordinated by P01 administrative cores that have facilitated communication among subprojects.

- P01s that have facilitated coordination across organizations – the Georgia Centenarians study (Lenny Poon), for example, has project leaders from across the U.S.

- Researchers involved in modeling systems working with scientists studying human cells to transition and translate their research.

- Economies of scale through sharing of data sets. For example, data collected on long-term care in hospitals and nursing homes, as well as the Panel Study of Income Dynamics funding for data collection, allow for an endless possibility of data analysis.

Interviewees also pointed out that in many cases, researchers are already collaborating before they receive their P01 grants and working relationships have already been established. Collaborative studies draw upon the expertise of scientists from many different disciplines and occur across multiple funding mechanisms, the P01 being one of them. Another example is the Claude D. Pepper Older American Independence Centers (OAIC) to increase scientific knowledge leading to better ways to maintain or restore independence in older persons. The OAIC "centers of excellence" are designed to develop or strengthen institutions' programs that focus and sustain progress on a key area in aging research. Each area of focus is one in which progress could contribute to greater independence for older persons and offer opportunities for training and career development in aging research. The Centers often collaborate with other Pepper Centers on complementary projects as well as with other institutions, NIA and NIH-supported resource such as research cores. Also, some ADCs have satellite facilities that offer diagnostic and treatment services and research opportunities in underserved, rural, and minority communities. The ADCs have also helped create additional collaborative research resources or projects, such as the Consortium to Establish a Registry for Alzheimer's Disease, the National Alzheimer's Coordinating Center, the Alzheimer's Disease Cooperative Study, and the Alzheimer's Disease Neuroimaging Initiative.

The Role of P01s in Providing Mentoring Opportunities

Even though P01s do not have mentoring components, with the different levels of investigators involved in P01 research, some experienced investigators have used the P01 mechanism for informally mentoring new/early stage investigators. Researchers mentored through P01s are also going on to get their own projects and funding. For example, Stanley Prusiner is a long-time P01 grantee and recipient of the 1997 Nobel Prize in physiology or medicine for his discovery of prions. As Director of the Institute for Neurodegenerative Diseases at the UCSF Memory and Aging Center, he has in turn been successful in mentoring two junior investigators, who are now leading successful projects of their own and receiving funding from NIA.

There are numerous other mentoring success stories coming out of P01 experiences. Shripad Tuljapurkar, Professor of Population Studies at Stanford University, directs demographic programs at Stanford's Center for the Demography, Economics and Health of Aging, and the Stanford Center for Population Research in the Institute for Research in the Social Sciences. Amy Finkelstein at MIT is working on public policy in the health care sector. Both have been involved in mentoring young investigators through their P01 work.

Input on the Review Process Used for P01s

Program Officer Perspective

The program officers we interviewed cited both advantages and disadvantages to the review process currently used for P01s. Advantages of P01s cited include the following.

- Review is in-house and the expertise of the reviewers is better in most instances than review through CSR committees. It is difficult for members of most CSR committees to be familiar with

the varied content covered by some interdisciplinary project descriptions and to understand their full potential. NIA's Scientific Review Program staff are able to select reviewers for a P01 application based on reviewer expertise and the content of a particular application.

- The period for questions before the review begins allows the scientific review staff to gather additional information for the special emphasis panel.

Interviewees also highlighted disadvantages.

- One concern was that because P01s are reviewed one at a time, there is no comparison point and less of a competition factor. Some scientific program staff believe that when a P01 is reviewed by an IC-specific review panel, different elements come into play and the success rate is higher for P01s than for R01s. There is no comparison to other P01s because each is handled separately on an ad hoc basis. Therefore, some scientific program staff believe that the quality of the review of P01s is not the same as the standing CSR section review.

Program officers also expressed a number of other concerns.

- While set-asides for P01s would be an option to pay for a percentage of the P01s, program staff need to step up and raise questions about whether it is right to have a new initiative funded in an emerging area when the payline is so low that the science that is already being funded may be discontinued in favor of the new initiative.

- "We do not say no enough." With a limited budget we should start thinning things back - e.g., there are certain applications that are not related to aging research and could be funded by another IC.

- A committee or group should be formed to triage P01 applications. There was not agreement concerning whether to have a select committee vs. a standing committee for applications to be reviewed adequately. Some suggested that having reviewers with varied expertise in aging would be needed and might be easier to accomplish on an NIA standing committee.

- From the perspective of some interviewees, the review process has been degraded now that NIA no longer has on-site reviews. Reviews are now conducted by phone and some believe that there is a significant loss of quality in the way that applications are reviewed now versus how they were reviewed 3-4 years ago. Because the P01 is a complex funding mechanism and requires much coordination, some interviewees thought it more beneficial to have the reviewers on-site where they could actually see the resources to be shared and visit the PIs. The in-person discussions bring insight into the reality of the collaboration, and reverse site visits for competing or amended grants are beneficial for reviewers.

Scientific Review Officer Perspective

We also talked with Scientific Review Officers who discussed their views of the P01 review process. They made the following points.

- Several years ago, NIA decided that any application (P01, P50, U01, Multisite R01, etc.) with substantial budget request (more than a few millions) should be site visited, and this was changed to reverse site visit (RSV) because of travel constraints. Within the last 2-3 years, because of tightening budgets, NIA moved away from RSV and instituted teleconference review which includes power point presentations followed by Q&A with the PI. This process is used for new and competing P01s, P30s, P50s, U01s, U24s, multi site R01s, and any other large

applications. These changes were instituted following extensive discussions with Division Directors and approval by Dr. Hodes.

- One of the challenges of P01 reviews is the large number of investigators involved in each project [~20], making the establishment of a review panel especially difficult. One issue in particular is the need to ensure that there is no conflict of interest between the members of the review panel and the investigators.

- Some of the advantages of a phone interview are that NIA can get Nobel laureates and top scientists as reviewers, logistical problems are much easier to handle, it is a much less expensive process than a site visit, more reviewers can be on the panel, and expertise in multiple relevant disciplines is easier to address.

- P01 scores have not in any way influenced (positively or negatively) or affected scores from other mechanisms such as R01/R21/R03, etc. because P01 scores are percentiled against the total CSR base (average of more than 200 study sections going back to the last three rounds). This is different from R01s, which are "percentiled" against one study section base. Moreover, it was the decision of the institute to consider P01 applications as being in the same RPG category as the R01 and R21.

- With regard to the issue of review by a select versus a standing committee, the Review Officers explained that special emphasis panels are critical to providing the needed reviewers. They mentioned that P01s have never been reviewed by standing committees because of the diversity of the research and the breadth of disciplines involved in aging research. A prior method involved a site visit report going to a standing committee who then voted the final score. The same standing committee received multiple site visit reports.

P01 Longevity and Productivity

Some scientific program officers believe that P01s continue to be productive regardless of longevity. They say that some have been hugely productive – and if they are not productive, this is reflected in the review process. Most P01s have provided tremendous amounts of information, but in terms of "bang for the buck," there was no general consensus as to whether NIA could get more benefits out of three R01s rather than one P01. All interviewees, however, agreed that if the science continues to evolve, then there are benefits to P01s because of the integration of various disciplines and the cost efficiency.

We also found differing opinions about how useful a P01 is after a certain period of time. Some think that P01s should have short half-lives, and others believe that they should "live out their natural lives." P01s change over time and must not operate within a vacuum. They are evaluated every 5 years, and as long as the research is solid, there is no question as to how long the project continues, as long as it gets through peer review.

One example is the Aging Nonhuman Primates (NHP) studies, which started in 1999 and are now a valuable resource supporting several projects that span various disciplines. Having a long-term outlook in place is needed to allow these studies to unfold over time and promote a multi-disciplinary approach to the use of the nonhuman primate models in aging research. First, Gallagher et. al. started out using rodents in early research and then expanded to nonhuman primates, putting very powerful models together and empirically testing them. So, there was a ramp up of activities after a five-year period and then the thinking started to coalesce. This study has now expanded beyond a P01 into a clinical trial.

Another example mentioned by DBSR staff was the "Oldest-Old Mortality: Demographic Models and Analyses" P01-AG-8761 led by James Vaupel. This P01 has been funded since 1990 because of successful renewals, but there has been a turnover of investigators through the years. So even though this is a long- running P01, the components are not the same as 20 years ago, and Christensen began a leading population genetics study out of the Vaupel P01. Another P01 led by Lillard has new investigators because the PI died and new components were introduced.

For renewals, some interviewees believe that a review by internal staff and division directors may provide a closer scrutiny than renewals are currently given. P01s are supposed to evolve but one problem is that there is no limit to funding a P01. How long should NIA keep investigators working together and at what point should there be a transition from a P01 to an R01 or to a U01 and vice versa?

Others believe that P01s have value especially for emerging areas of science because they provide the proper environment for synergy, but there must be a limitation to two cycles similar to the merit awards. They believe that the main criteria for accepting a P01 should be integration and collaborations that would not happen otherwise, and then there should be a sunset so that new ideas and new investigators are given a chance to flourish.

Comparison of long-term P01 and R01 grants

Creating datasets

Three data sets were created to compare P01 and R01 grants. The first set, which we called short-term P01s, included 30 P01 grants funded by NIA between 1990 and 2010 with one or two renewals. The second set, long-term P01s, included 28 grants which had been awarded four or five renewals. The third set contained 31 longest running NIA R01 grants available from QVR.

Obtaining data on P01 and R01 grants in the datasets

Data were obtained from eSPA and QVR databases. The grant sets described above were used to create portfolios in eSPA. The portfolio function in eSPA allows the compilation of specific information on individual grants contained in each dataset. Each portfolio contained data on the numbers and dates of publications, duration of grant, funding amount, impact factors, number of citations, and number of patents. These data were exported from eSPA to Microsoft Excel and used for statistical analyses.

Characterization of datasets

Exhibit 14 presents descriptive statistics for the three datasets. The sets are similar in the total number of grants, and the two long-term sets are also similar in total and per grant funding duration. However, long-term P01 grants received roughly three times as much total funding as either short-term P01 or long-term R01 grants, both collectively and per grant.

Exhibit 14: Description of P01 and R01 sets of grants used in analysis

	Short-term P01s (1-2 renewals)	Long-term P01s (4-5 renewals)	Long-term R01s (4-5 renewals)
Number of grants (counts)	30	28	31
Total duration (years)	303	760	875
Minimum duration (years)	7	21	23
Maximum duration (years)	13	40	49
Average duration (years)	10	27	28
Average duration from grant start to 2011	15	27	26
Total funding (dollars)	$279,103,273	$766,466,490	$208,201,109
Average funding per grant ($)	$9,303,442	$27,373,803	$6,716,165

Data sources: eSPA and QVR

Analysis of total grant productivity

For each grant, we obtained the total number of patents, publications, citations to each publication, and impact factors for each journal in which the publication appeared. Exhibit 15 presents data for the three sets of grants. The number of publications resulting from long-term P01s was three times the number of publications resulting from long-term R01s. This may be due to the fact that P01s typically include at least three participating PIs holding an R01-sized subproject each. Using numbers of publications as a measure, productivity of long-term P01s was 3.6 times higher than for short-term P01s. This difference is again expected, given that long-term P01s were funded for an average of 27 years versus 10 years for short-term P01s (Exhibit 14).

More informative comparison can be made between the sets normalized to dollar amount, number of years, and number of grants. Long-term R01s appeared to be slightly more productive with 8 articles per $1 million compared to 7 for long-term and 5 for short-term P01s, respectively. Long-term R01s had significantly higher impact as measured by the number of citations: 137 citations per article for R01s versus 40 for long-term P01s and 29 for short-term P01s. However, long-term P01s had 3.5 times higher average number of publications per grant year than long-term R01s, and 1.4times higher average number of publications per grant year than short-term P01s.

Journal Impact Factor is often used as a measure of article influence. Impact Factors for most journals range between 4 and 6, but can be as high as 30 for top tier journals such as *Science* and *Nature*. All three sets of grants that we examined had similar journal Impact Factors of approximately 5. Note that

because the vast majority of impact factors for biology journals are less than 5, an Impact Factor of 4.3 places a journal in the top 25% of all biomedical journals.[2]

Comparisons can also be made between long-term and short-term P01s. Short-term P01s emerged as somewhat less productive in publication counts per $1 million (5 versus 7) and per grant year (also 5 versus 7, Exhibit 2). Further, short-term P01s were also lower in the number of patents per $1 million (0.03 versus 0.09). Finally, short-term P01s had lower number of citations per article (29 versus 40) but similar average journal impact factors (5.3 versus 5.1).

Exhibit 15: Productivity of P01 and R01 grants

	Short-term P01s (1-2 renewals)	Long-term P01s (4-5 renewals)	Long-term R01s (4-5 renewals)
Total number of publications	1,519	5,424	1,756
Average number of publications per $1 million	5	7	8
Average number of publications per grant	51	194	57
Average number of publications per grant year	5	7	2
Total number of citations (self-citations excluded)	43,532	215,937	239,949
Average number of citations per article	29	40	137
Total number of patents	7	68	3
Average number of patents per $1million	0.03	0.09	0.01
Average impact factor	5.3	5.1	5.2

Data source: eSPA

Analysis of productivity over the course of the grant

The number of publications for P01 and R01 grants were calculated in 5 year increments anchored to the funding start date. Two types of analyses were performed: (a) productivity for long grants, funded for at least 20 years and (b) productivity for very long grants, funded for at least 30 years (Exhibit 16). Panel A shows productivity for long P01s, long R01s, and short P01s. As the reader can see, the number of publications increased for all three sets of grants over the period examined.

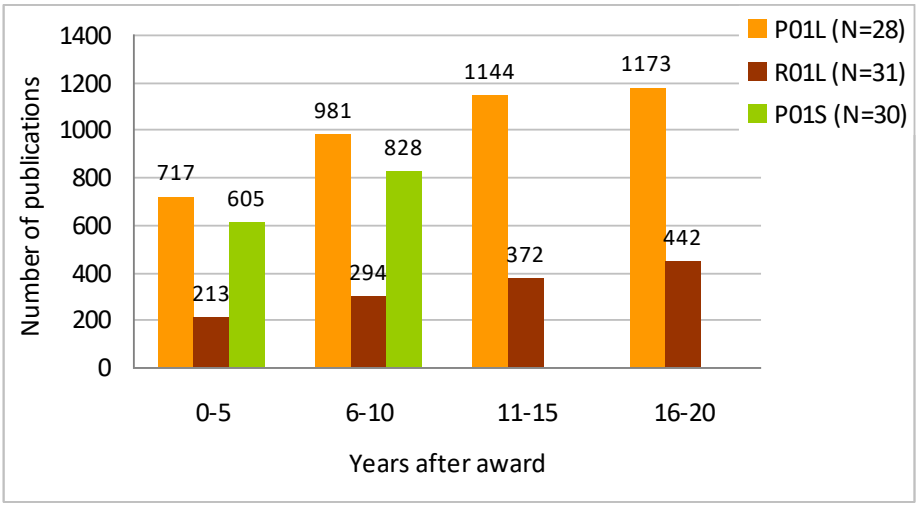
Two subsets of P01s and R01s were then constructed to investigate even longer-term productivity trends. These "very long" grants were funded for at least 30 years and included 9 P01s and 9 R01s. (While some of the grants were funded for as long as 40 years, the number of publications after 30 years

[2] Stephen J. Bensman. Distributional Differences of the Impact Factor in the Sciences Versus the Social Sciences: An Analysis of the Probabilistic Structure of the 2005 Journal Citation Reports. *Journal of the American Society for Information Science and Technology*, 59(9):1366–1382, 2008.

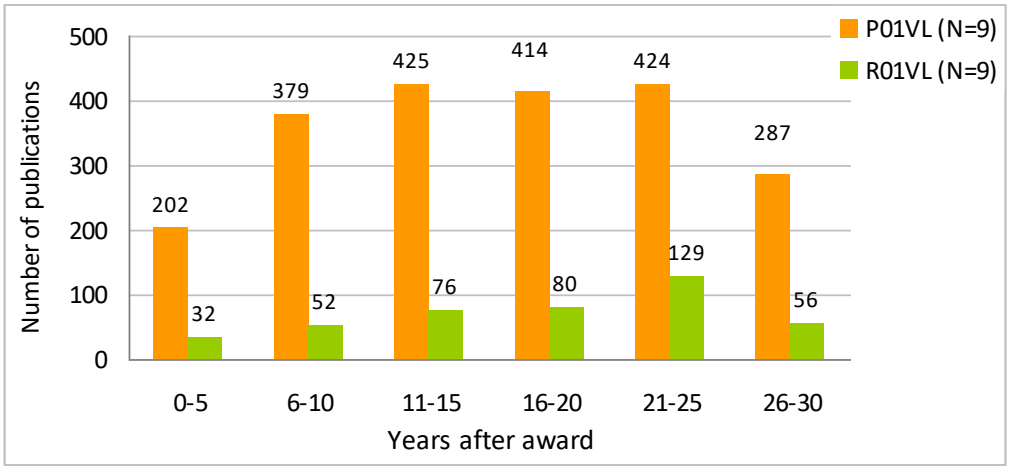
is not shown because the number of grants was too small too yield meaningful data.) This analysis showed that the level of productivity continued to increase for the first 25 years, similarly to the full set shown in 16A, and then decreased dramatically for both P01s and R01s (Exhibit 16B). The number of publications fell by 1.4 fold for P01s and by 2.3 fold for R01s.

Exhibit 16: Number of publications over the course of 20 and 30 years

A. Long P01s and R01s and short R01s



B. Very long P01s and R01s

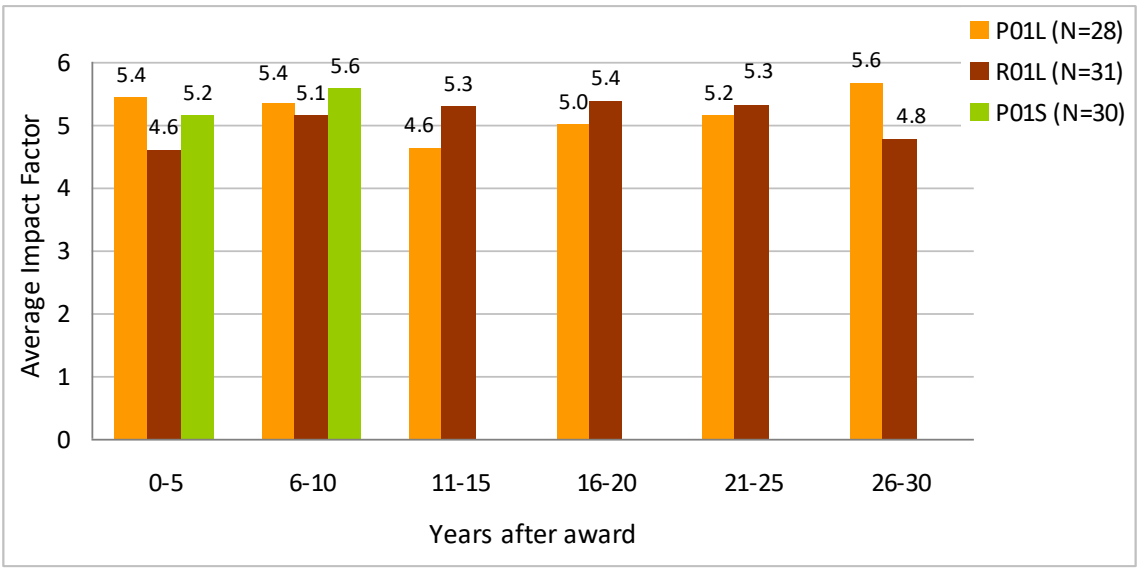


P01L and R01L: grants funded for at least 20 years
P01S: grants that were funded for only 10 years
P01VL and R01VL: grants that were funded for at least 30 years
Data Source: eSPA

Analysis of impact over the course of the grant

The change in average Impact Factors over time for the three sets of P01 and R01 grants was calculated. Note that approximately 10% of journals did not have Impact Factors, and the calculations of the averages were correspondingly adjusted. Similar to the publications, Impact Factor data are presented in 5-year increments ranging from 0-5 to 26-30 years (Exhibit 17). The results showed that Impact Factors changed little over time. The apparent decline in the R01 Impact Factors for the last time period could be due to small sample size, as only 34 publications were in this set.

Exhibit 17: Journal Impact Factors over time



Data source: eSPA

Conclusions

Our comparative analysis of research productivity between P01 and R01 grant mechanisms resulted in the following findings:

- The number of publications per $1 million of funding was similar for the three sets.
- The average number of citations per article was significantly higher for long-term R01 than for P01 grants.
- Long-term P01s produced significantly more patents than R01s or short-term P01s.
- Impact factors for all three mechanisms were similar and changed little over time; the average impact factor places the publications in the top 25% of biomedical journals.
- The number of publications for very long P01s and R01s continued to grow for 25 years after the initiation of funding and then declined; the number of publications for short-term P01s continued to grow for the duration of the grant.

Based on these data, we conclude that longer-term P01 grants were more productive than short-term P01s in the number of publications and patents per grant, per grant year, and per unit of funding. Comparison between long-term P01s and R01s did not show significant benefits of P01 over R01 funding mechanism, other than in the number of patents. Papers resulting from R01 grants were significantly more cited than papers resulting from P01 grants, despite similar average length of time from the grant initiation to present for the two long-term grant sets.

Appendix

QUOTES from NIA Program Staff Regarding the Use of the P01

- "P01s are very important in terms of programmatic development and provide important scientific information; so there is no need to put a time restraint on them. However, they should be looked at in terms of dollars and science, and NIA should probably have fewer P01s."
- "The mechanism is a great tool to promote interdisciplinary research. We need more of the coordinating mechanisms. So when you have years and years of study, a P01 awarded in 2000 has definitely helped advance research on cognitive decline for example. However, we should be more active in slashing some of the P01s.
- "A 44% success rate is unusual. Can we increase competition to enhance review? Triage at the front end is a possibility – perhaps establish a standing committee that is not too close to the specific area of research and would look at all factors critically."
- "P01s are fine as they are."
- "P01s have been effective in getting the magnitude of research that has been proposed in each of them. It is difficult today to get them reviewed adequately in regular CSR study sections."
- "A better P01 review would be an "in person" review. Telephone reviews have drawbacks and sometimes discussions tend to cycle in the negative because of time constraints. There are strengths and weaknesses in a site visit, but if we are going to invest that much money, we should make sure the review is as good as possible."
- "This is a useful mechanism, but to get better results, the criteria for the review should be enhanced, and funding should be limited."
- "Each division should have a limited amount of dollars to fund P01 applications. Right now, there is no limitation; so many P01s are funded. When the budget is tight, P01s compete with the large R01s. So divisions will have to choose between $500K level funding and more R01s versus P01s at $1.5 M."

Results of Initial Discussions with Extramural Division Representatives

What are the reasons why you would fund P01 applications/what outcomes would you expect?

Reason/Anticipated Outcome	*Related Evaluation Questions*	*Possible Measures*
Promote interdisciplinary science.		
DGCG: Promote interdisciplinary science. Develop leadership teams. **DAB:** Bring together diverse expertise around a common issue. **DN:** Bring together a team with diverse talent and resources. Encourage integration of methodology and scientific disciplines. Get at different aspects of a problem. Solve an important/difficult problem. **DBSR:** Be able to build around a central or core study. Develop a critical mass of thinking. Support the use of multilevel approaches – e.g., applied and basic, micro-macro-molecular. Increase interdisciplinary integration between the behavioral and social and the biological.	Were interdisciplinary teams formed? From what types of institutions did they come (e.g., medical schools, schools of engineering)?	The interdisciplinary makeup of the teams as described in applications and progress reports
	How successful were the teams in working together?	Anecdotal evidence of team success based on success criteria and interviews with POs and/or PIs concerning
	Were connections made as a result of the project that would not otherwise have been made?	Specific examples of connections made and descriptions of successful interdisciplinary efforts from interviews with POs and/or PIs citing
	Is there evidence that research supported through P01s could not have been funded through other mechanisms?	Comparative assessment of examples of similar projects identified through database searches or through interviews with POs and/or PIs to determine how they compare in terms of the quality of scientific integration, etc.
	What do we need to do to make it work better?	A roll-up of suggestions from interviews with POs and/or PIs
Facilitate high quality research.		
DGCG: Obtain tight/cohesive answers to important research questions.	Have P01 researchers made significant contributions to their fields? What findings resulted after 5, 10 years of study? Are P01s that have been funded for 15 years or longer still productive?	Numbers of publications, journal impact, citation patterns as determined through bibliometric analysis of P01 project publications

DBSR: Facilitate quality research. Generate higher impact publications.	Were these advances recognized by NIH/NIA as being of special significance?	Numbers of advances highlighted in NIH/NIA press releases, reports, stories of discovery, and other documents.
Launch new areas of research, quickly build up existing areas, or expand in new directions.		
DGCG: Area of research jumpstarted or moved forward. Jump start to an area of research. **DN:** Quickly build synergy around an area of needed research. Develop new fields of study. **DAB:** Build synergy.	What new areas of research have been jumpstarted or expanded in new directions as a result of P01 funding as compared with other mechanisms?	List of new/expanded areas tracked to P01s – e.g., biodemography, autophagy.
		Comparative list of new/expanded areas tracked to other mechanisms.
Provide needed infrastructure to support large, complex research projects.		
DGCG: Provide for infrastructure needs, access to data, etc. **DAB:** Support cores for project integration. Support cores as a possible resource for other projects. **DBSR:** Support cores to increase productivity and coordinate across subprojects. Support cores to increase efficiency in analysis and provide support to meetings.	Have cores been successful in helping to integrate the work of subprojects?	Example descriptions of services provided, obtained from applications, annual reports, and interviews with POs and PIs
	Have cores provided the needed data management support?	Examples of data archives and management activities obtained from annual and other reports and publications and from interviews with POs and PIs.
		Comparative examples from projects funded with other mechanisms.
	How about data, equipment, and other resource sharing?	Examples of sharing/leveraging activities obtained from annual and other reports and publications and interviews with POs and PIs.
Provide mentoring and training opportunities.		
DGCG:	How many of our P01 grants include mentoring and training components?	Numbers of project descriptions citing these components

Maybe provide training or mentoring opportunities. **DBSR:** Provide a good training ground for young or new investigators.	What is the track record for P01 projects' producing investigators who continue careers in aging research?	Numbers of young/new investigators who go on to receive K, R, T, or even P awards as determined through searches in QVR or other data sources
		Comparative numbers associated with other funding mechanisms
		Anecdotal success stories obtained through interviews with POs and PIs
Move science along the translational/translation continuum.		
DGCG: Move discovery more quickly from basic to translational and make interventions successful in practice (the ultimate). Gain understanding with potential for development into a new intervention. Develop tools for future studies. **DAB:** Increase our potential to facilitate translational research. Generate more options for testing reproducibility. Yield meaningful results.	Have P01s generated more research that led to translation than other mechanisms?	Percent of projects that have led to intervention development/testing/etc.
		Especially significant examples of interventions coming out of P01 projects with descriptions of why they were deemed successful.
Attract top researchers to aging research, especially in areas not typically viewed as aging related.		
DBSR: It is one of the most effective ways to recruit top young researchers to aging research and people who would never come to us otherwise.	Has the P01 mechanism been successful in attracting top scientists into aging research?	Numbers of top scientists participating in P01 projects as identified by POs and broken down by discipline
	What has the impact been to the field of aging research?	Examples of high reward research with descriptions of how the P01 was instrumental in drawing investigators to the field, as described by POs
		Comparative examples of the same through other funding mechanisms, as described by

		POs
Build relationships for future collaboration.		
DGCG: Make connections for possible collaborations. Spin-off related work involving the same collaborators Create synergy for other work. **DN:** Build synergy across NIA divisions. **DAB:** Establish potential to facilitate collaborations.	Did other projects follow involving the same collaborators?	Follow-on funding of the same team as identified through QVR or similar sources ("off-spring" grants)
	Have collaborations among sub-projects persisted beyond the duration of P01s?	Follow-up funding history of the collaborating investigators tracked through QVR or similar sources
	What new connections/collaborations resulted from the project?	Examples of collaborations identified in research or publication databases or from interviews with POs and/or PIs
Allow for an easier/better application and review process.		
DAB: We are able to use a different review process. We have the opportunity to influence the makeup of the review group. **DBSR:** We are able to conduct the right kind of reviews with the right kind of reviewers. There is no need for an FOA as a team of researchers to examine a problem comes with the P01 project. This is especially valuable for applied areas of research.	Has the different review process and reviewer selection procedure made a difference in the quality of reviews and resulting funding decisions for P01s?	Descriptive information from POs
	How do P01 teams compare with networks of investigators that have been assembled using an FOA?	Descriptive examples of P01 and FOA assembled teams/networks with evaluative input from POs – and perhaps participating PIs

Questionnaire for Program Officers

Scientific Progress

- In your experience, what have been the advantages/disadvantages of combining subprojects into a P01 versus pursuing each project separately using the R01 or other mechanism?
- Can you cite some significant examples of new scientific opportunity where synergy has been built through P01 supported research?
- What new areas of research are you aware of that have been jumpstarted or expanded in new directions as a result of P01 funding as compared with large R01s?
- Have you seen progress made in creating new methods, new scientific models, and new interventions as a result of P01s?
- Can you cite examples where P01s have led to valuable scientific outcomes that would not have occurred without the collaborative structure of the program project?
- Have you seen P01 projects more rapidly or successfully move research beyond basic research to pre-clinical research or application in a clinical trial? Into medical practice or public health programs? If yes, to what would you attribute the success?
- Can you provide examples of ways in which P01s have provided the infrastructure for following cohorts over long periods of time? Could this have been done just as effectively with other funding mechanisms?

Communication and Coordination

- Have P01s increased the emphasis on cross-disciplinary approaches to research and support to data management?
- Have P01 projects been successful in encouraging interdisciplinary research and helping investigators work together?
- Have groups from different organizations (ICs, agencies, etc.) and disciplines started working together as a result of P01s?
- Can you cite examples where better communications, information dissemination, and connections were established as a result of P01 interactions?
- Have P01s resulted in formal as well as informal collaborations among researchers in various disciplines?

Infrastructure

- Can you cite instances where P01s have been especially successful in providing the infrastructure for leadership, collaborative activities, and resource sharing?
- Have cores been successful in helping to integrate the work of subprojects and capitalize on the strengths of different subgroup projects?
- Would you say that the P01 mechanism has proven to be more effective, as effective, or less effective than large R01s in supporting large scale research projects?

Paradigm Shifts

- Have you seen evidence that participation in P01s may have stimulated researchers to change their approach to research, the way they pursue ideas, etc.?
- Has the different review process and reviewer selection procedure made a difference in the quality of reviews and resulting funding decisions for P01s?
- Is there clear "value added" in conducting P01 research over large R01s?

Influence

- Can you provide examples of situations where the P01 mechanism has been successful in attracting top scientists or young investigators into aging research?
- How about examples of times when other projects have followed involving the same collaborators? Did those researchers build on existing initiatives/programs?
- Can you provide examples of how experienced investigators have used the P01 mechanism for mentoring new/early stage investigators?
- How about situations where collaborations among sub-projects have persisted beyond the duration of a P01 grant?

Impact

- Can you cite examples of how P01s have impacted the field of aging research over time? Are there comparable achievements through the R01 mechanism?
- Can you provide examples of ways in which P01 grants have helped move research along the basic-translational-clinical-application continuum? To what would you attribute this success? What might make this work better? Are there comparable success stories with R01 grants?
- Would you say that P01s have made a significant contribution to improving health and well being that would not have been as likely through large R01s? If yes, in what ways? If no, why not?

Future Outlook

- How would you describe the effectiveness of P01s in terms of return on investment?
- Are there benchmarks for success in accomplishing the specific aims of the P01 mechanism?
- What do we need to do to make P01s more effective?

Most Cited Articles Published by P01 Grantees

Project Number	Article Title	Pub. Date	Times Cited
P50NS014069, P01AG002132	Novel proteinaceous infectious particles cause scrapie.	04/1982	1,916
P01AM030582, R01AM027065...	Involutional osteoporosis.	06/1986	1,528
P01AG017625	Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.	12/2002	1,485
P01AG002219	A new rating scale for Alzheimer's disease.	11/1984	1,299
P01AG003991	The Clinical Dementia Rating (CDR): current version and scoring rules.	11/1993	1,187
P01NS022786, P50NS014069...	Molecular biology of prion diseases.	06/1991	1,067
P01AG000538, R01NS031230...	Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis.	04/2003	1,019
R35AG010963, P01AG007232...	Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease.	08/1996	1,000
P01AG012992, R01NS033958	Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate.	03/1996	980

Data source: eSPA

Top 10 P01s by Cumulative Award

Project Number	Project Title	Total Award
P01AG002132	Degenerative and Dementing Diseases of Aging	$46,733,455
P01AG007232	Epidemiology of Dementia In An Urban Community	$40,531,208
P01AG003991	Healthy Aging and Senile Dementia	$38,789,600
P01AG003949	Einstein Aging Study	$35,671,464
P01AG005842	Economics of Aging	$35,305,356
P01AG002219	Clinical and Biological Studies of Early AD	$35,189,877
P01AG000001	Neural Substrates of Cognitive Decline in Aging Monkeys	$33,535,135
P01AG001751	Gene Action in the Pathobiology of Aging	$32,173,538
P01AG004875	Physiology of Bone Metabolism in an Aging Population	$31,857,421
P01AG010770	Molecular Pathogenesis of Age-Dependent CNS Degeneration	$30,795,947

Data source: eSPA

Evaluation of the R21 Funding Mechanism at the National Institute on Aging

Background

As stated in Program Announcements, the goal of the R21 funding mechanism is to "Encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects." Solicitations state that: "These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research."[1] R21 grants are limited to two years, with a combined budget for direct costs usually not exceeding $275,000 and these grants are non-renewable. The NIH uses two types of solicitations to fund R21 grants: cross-agency "parent announcement" and FOAs originating from individual institutes and seeking proposals in specific research areas. Prior to 2003 when the first parent announcement PA-03-107 was issued,[2] the R21 mechanism was used exclusively in FOAs. PA-03-107 redefined the R21 mechanism to allow investigator-initiated applications. The current parent announcement expires in January 2013.

It is clear from the parent announcement that the R21 mechanism is meant to be a seed grant for high risk research, to give investigators at all career levels an opportunity to examine the feasibility of an innovative idea. Over time, however, the R21 mechanism came to be viewed by the scientific community as a stepping stone for junior investigators to their first R01. Concerned staff at NIH institutes began to discuss the goals and utility of R21s with their Advisory Councils.[3] Some, like NINDS, started to discourage young investigators from applying for R21s, noting that success rates for these grants were lower than for R01s and that this mechanism was not meant to be a launching pad for an R01.[4] Other ICs made changes to their R21 programs. For example, NIAMS staff considered withdrawing from the parent program in 2010. The Institute staff ultimately decided to continue participating, but to reshape the program by stressing innovativeness and the high impact nature of the research, and by encouraging the applicants to consult with the Institute before submitting a proposal (presumably to discourage non-innovative ideas).[5] Six NIH institutes have stopped participating in the parent PA, although they continue to use the R21 mechanism to support their own programs. This group includes FIC, NCI, NCMHD, NCRR, NIGMS, and NHLBI.[6] NHLBI staff performed the analysis of the Institute's R21 portfolio and determined that early-career investigators were half as successful in obtaining R21s as established investigators, but the success rates were similar for R01s.[7]

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[1] NIH Exploratory Developmental Research Grant Program (Parent R21). PA-10-069

[2] http://grants.nih.gov/grants/guide/pa-files/pa-03-107.html

[3] Minutes of Advisory Council Meeting. NIAMS, 2008 and 2009.

[4] http://blogs.sciencemag.org/sciencecareers/2010/05/ninds-to-new-in.html

[5] Minutes of Advisory Council Meeting. NIAMS, 2009.

[6] http://grants.nih.gov/grants/funding/r21.htm.

[7] Hannah Waters. Exploratory grant scheme abandoned after failing to meet its goals. *Nature Medicine*. 17(8):903. August 2011.

Purpose of the Evaluation

The leadership at NIA has decided to examine the Institute's R21 portfolio. The main impetus for the evaluation is the decline in the number of R21 grants awarded by NIA, which began in 2007, but NIA staff is also interested in other aspects of the R21 program, including expenditure, distribution across NIA and success rates. The Office of Planning, Analysis, and Evaluation (OPAE), with support from Abt Associates, conducted this assessment of R21 funding mechanism at NIA.

Methodology

The evaluation plan included research questions, data sources, and comparison groups. The plan was reviewed by Robin Barr at DEA and all suggestions were incorporated into the evaluation design.

Research questions

We attempted to answer the following questions:

1. What are the characteristics of the R21 portfolio at NIA?
    - What have been the trends for the number of grants, expenditures, success rates?
    - What types of institutions have received the grants and where are they located?
    - What percentage of the grants was funded through the parent announcement vs. RFA?
    - What is the distribution of R21 grants across NIA Divisions?
2. What is the nature and extent of the decline in the number of R21 grants awarded by NIA and NIH?
    - Can the decline be localized to a specific NIA division?
    - Have other ICs shown the same pattern?
    - Why did five other ICs stop participating in the parent R21 program? What, if any, analyses did these ICs conduct to reach this decision?
3. What have been the outcomes of the R21 awards?
    - How successful have R21 grantees been at obtaining R01s than individuals who did not have R21 grants?
    - What has been the grantees' level of productivity and impact?
    - What are the returns in productivity and impact per dollar invested? How does this compare with other funding mechanisms?
    - Do R21 applications score better on average than other applications on the Innovation criterion? Does the Innovation criterion weigh more heavily in the impact rating for R21 applications than for other applications?

Extant sources

Raw data was abstracted from QVR and eSPA databases as well as from the publically available NIH RePORTER database.[8] For each chart in the report, we specify its source, period, and sample size. We also comment on data issues in the relevant parts of the report. Finally, we obtained relevant data from the NIH website and reviewed prior studies of R21 program and similar grant mechanisms.

Comparison groups

We considered several comparison groups as possibilities for this evaluation. For each comparison mechanism, similarities and differences were summarized and presented to the NIA DEA staff for input. Possible comparison programs and final choices are described in Exhibit 1.

Exhibit 1. Possible comparison groups

Group	Similarity to R21	Difference from R21	Disposition and reason
R01	• Investigator-initiated • Supports independent research project	• No emphasis on exploration • Usually awarded for 3-5 years • $250,000 per year in direct costs	*Useful indicator of funding trends; the most common mechanism at NIH.* Not focused on innovation. Renewable. Significantly higher funding levels and project duration.
K99/R00	• Shared goal of competitiveness for R01 • Phase 2 (R00) is for independent research project	• Phase 1 (K99) is for mentored research project • PI does not have to be a US citizen • Phase I - $110,000 Phase 2 - $249,000 per year in direct costs	*Not a good comparator.* Phase 1 is a mentored award. Focus on new investigators rather than new science. Heavily concentrated in the basic sciences.
R03	• Limited to 2 years of funding • Not renewable • Exploratory in nature	• Up to $50,000 a year in direct costs	***Good comparator.*** It is smaller in funding levels, but this can be taken into account. The number of awards and coverage across areas is similar to R21.
NIH Director's Pioneer Award	• Somewhat similar in supporting exploratory, high-risk work • Not renewable	• Up to $500,000 a year for 5 years in direct costs • Has to propose ideas substantially different from those already being pursued by PI • Highly competitive; only a few awards cross-NIH • Support is meant for exceptionally creative	*Not a good comparator.* Unlike R21, focused on junior investigators. Significantly higher funding level and longer project duration. New program with few awards.

[8] http://projectreporter.nih.gov/

Exhibit 1. Possible comparison groups

		individuals	
NIH Director's New Innovator Award	• Aimed at early stage investigators • Exploratory • Not renewable	• Up to $300K a year for 5 years in direct costs • Support is meant for exceptionally creative individuals	*Not a good comparator.* Focused on junior, investigators. The R21 is open. About six times the allowable cost for an R21. Finally, recent program with few awards.
Transformative R01 Program	• Exploratory, support for novel concepts and creative ideas • Not renewable	• $250K+ per year in direct costs • Proposals have to demonstrate potential for major impact	*Not a good comparator.* Significantly higher funding level and longer project duration. New program with few awards.
NIH Director's Early Independence Award	• Meant for exceptional junior scientists, who have already established a record of innovation and research productivity, to launch an independent research program • Not renewable	• For MDs in the end of residency or PhDs in the end of graduate studies (similar to K awards) • Institutional award • Up to $250K a year for 5 years in direct costs	*Not a good comparator.* New program, few if any awards.

Feedback from NIA

The report draft was shared with NIA division staff members, who were asked to provide comments. We included some of the analyses proposed in this version of the report, and suggestions from division staff were incorporated in the concluding section.

Findings

In this section, data is presented and discussed as it relates to the research questions stated above. Whenever possible, comparisons are made to the R03 funding mechanism. In some cases, data on R01 grants are also presented, since the large number of R01 grants makes this funding mechanism a useful indicator for funding trends at NIA.

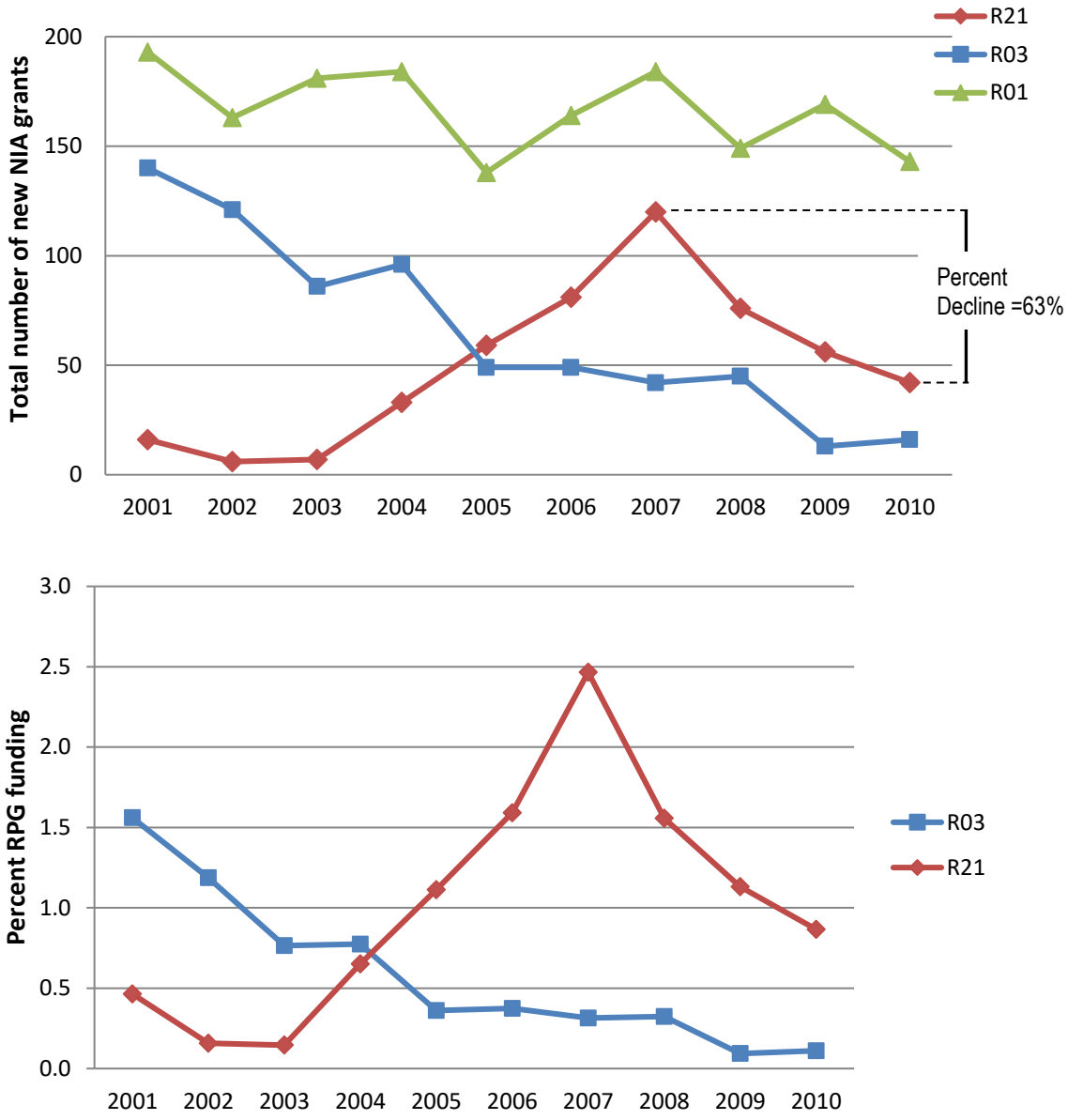
Characteristics of NIA R21 portfolio

The results show that the number of R21 grants funded by NIA and the relative total dollar amount spent on this mechanism began to decline in 2007 and continued to decline precipitously (Exhibit 2). Total expenditures on R21s declined as well (data not shown). Because this decline could be reflective of the general funding trend at NIA, we examined the patterns for R03 and R01 grants over the same period. It emerged that the number of R03 grants and the relative expenditures on this mechanism also declined over time, although the trend appeared to be more gradual (Exhibit 2). Note that over the period of 10 years, the decline of the R03

program has been very significant. The number of R03s decreased from 140 to 16 and the relative funding from 1.6% to 0.1% (Exhibit 2). For R21s, the number of grants as well as the relative expenditures actually increased since 2001. We presume that the dramatic increase in the number of R21s between 2003 and 2007 was the result of opening the R21 mechanism to investigator-initiated proposals.

R01 grants experienced fluctuation in numbers between 2001 and 2010 (Exhibit 2) and in total funding (data not shown), but overall remained relatively flat. To get a quantitative measure of the decline, we calculated percent difference between the number of grants awarded in 2007 and in 2010 (Exhibit 2) and found that R21 declined by 63%, R03 by 44% and R01 by 2.4%.

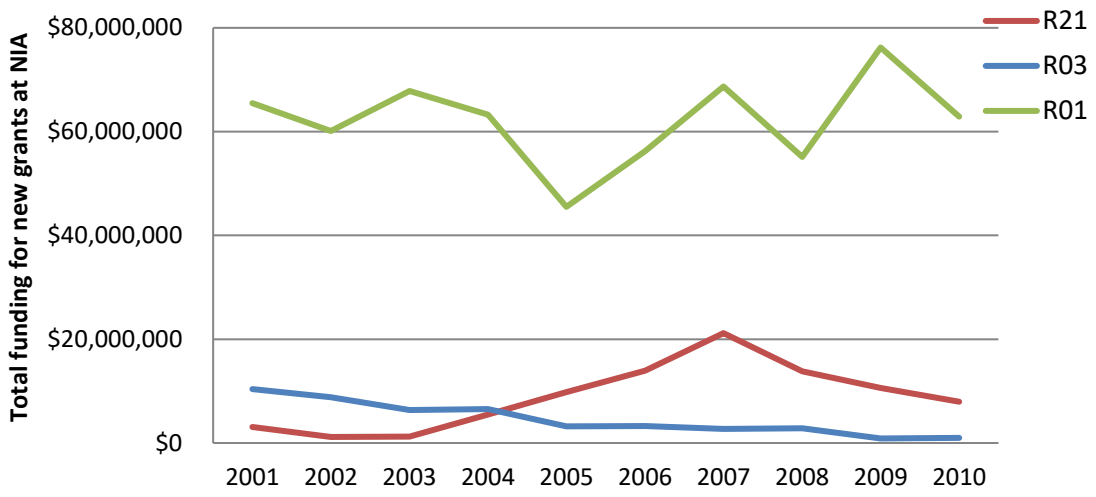
Exhibit 2. Number of R21, R03, and R01 grants at NIA and relative funding for R21 and R03 grants over the past 10 years.



Data Source: RePORTER

We also examined the NIA expenditures on R01, R03, and R21 grants for the past 10 years. Exhibit 3 shows that R01 expenditures significantly exceeded that of the other two mechanisms, and followed closely the trend seen for the number of grants awarded in Exhibit 2.

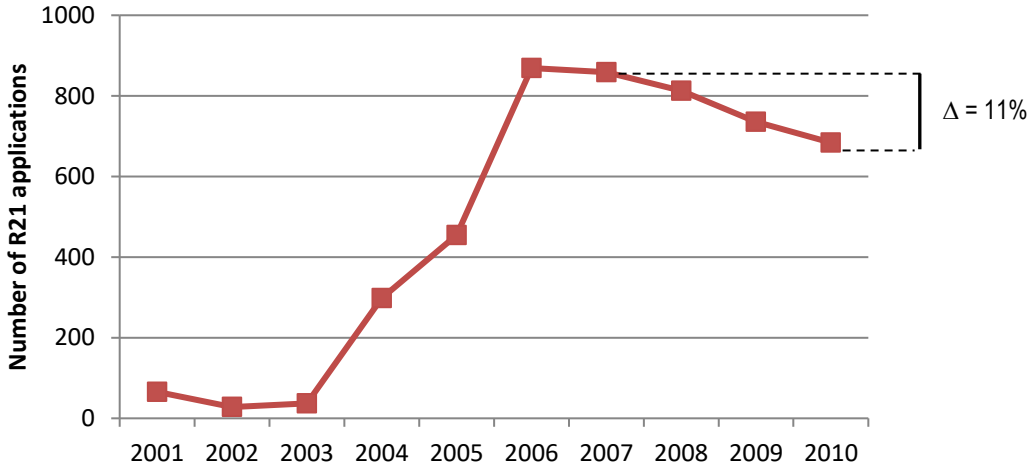
Exhibit 3. Total expenditures for new R21, R01, and R03 grants at NIA, 2001-2010.



Data Source: RePORTER

The decline in the number of grants can be the result of lower number of applications and/or of the increased funding mechanism competitiveness. We found that the number of applications remained relatively stable: it declined by 11% compared to 63% in the number of awards (Exhibits 2 and 4).

Exhibit 4. Number of R21 applications received by NIA, 2001-2010.

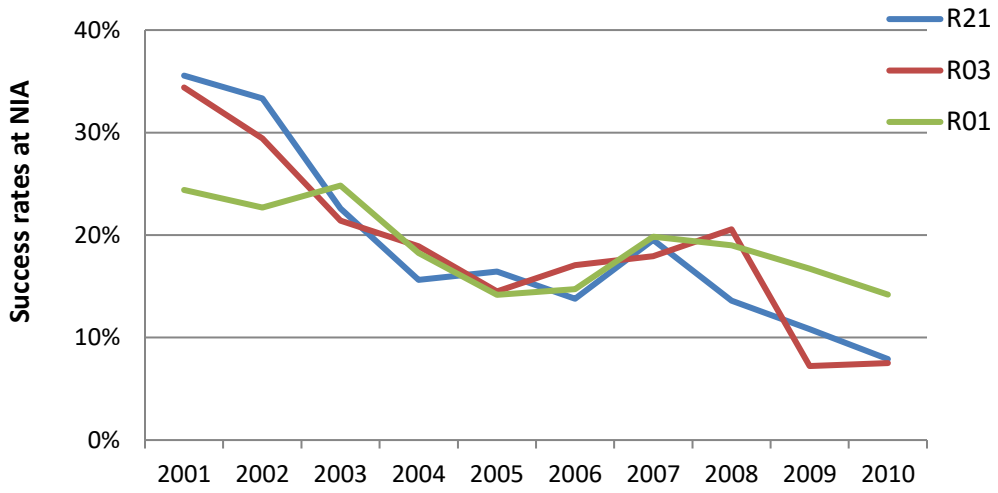


Data Source: QVR. Provided by Dr. Bhattacharyya.

This data suggests that the R21 funding mechanism has become more competitive. In fact, we found that R21 success rates fell from 20% in 2007 to 8% in 2010 (Exhibit 5). Therefore, at NIA, R21 awards decreased by 63% while applications fell 11%.

R03 and R01 success rates also declined over this time period, by 10% and 5%, respectively. This trend is consistent with the decrease in funding success rates across NIH.

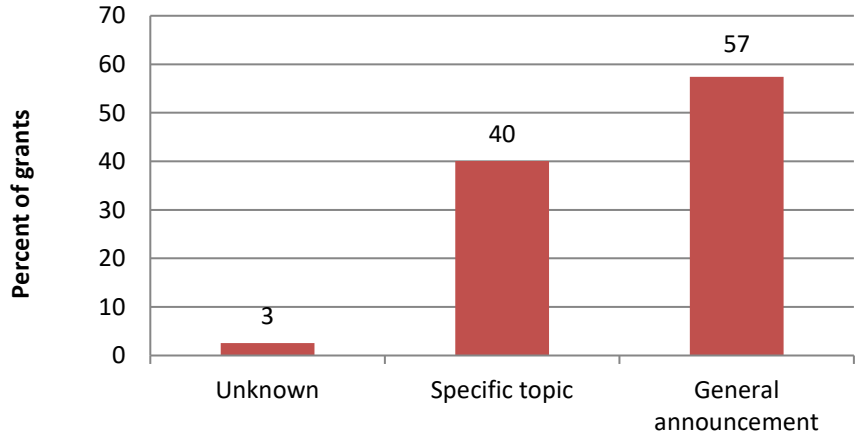
Exhibit 5. Success rates for NIA R21, R03, and R01 grants, 2001-2010.



Data Source: RePORTER

As mentioned in the introduction, NIH uses the R21 mechanism to support applications submitted in response to the parent announcement and to research topic-specific RFAs. We investigated the ratio of grants funded through these two types of funding solicitations at NIA. Between 2004 and 2010, almost 60% of R21 grants were awarded in response to the parent announcement (Exhibit 6).

Exhibit 6. Distribution of NIA R21s by type of announcement, 2004-2010 (N=514).

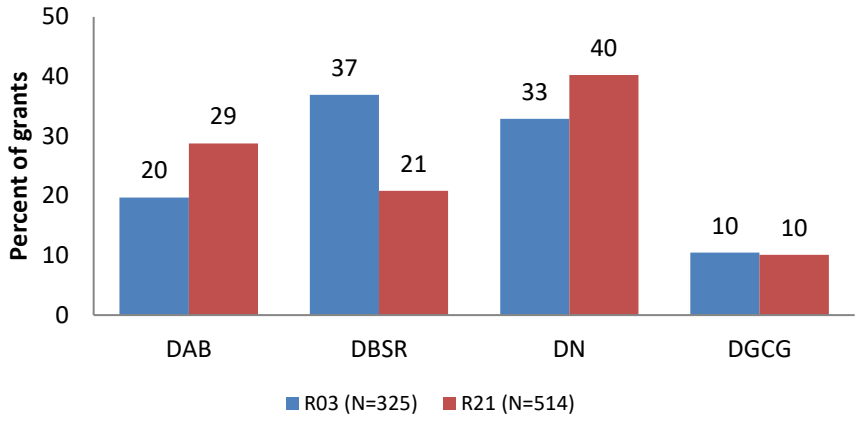


Data Source: QVR

NIA is divided into four Divisions based on research focus: Division of Basic Biology (DAB), Division of Neuroscience (DN), Division of Behavioral and Social Research (DBSR), and Division of Geriatrics and Clinical Gerontology (DGCG). All four Divisions support extramural research. We examined the distribution of R21 grants and comparison R03 grants by NIA Division. As Exhibit 7 shows, the Division of Neuroscience was the top funder of R21s (40% of all grants), followed by

DAB (29%). The distribution was somewhat different for R03s, with DBSR funding more R03s than R21s.

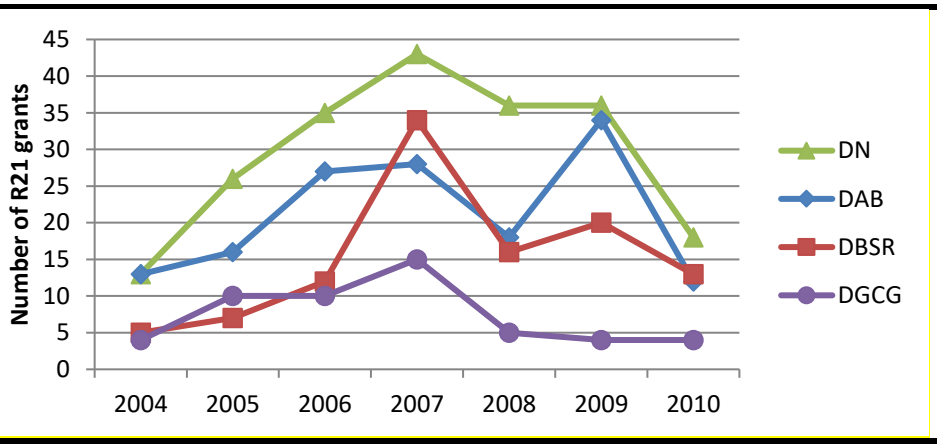
Exhibit 7. Distribution of NIA R21 and R03 grants by Division, 2004-2010.



Data Source: QVR

As discussed above, the number of R21 grants awarded has declined beginning in 2007 (Exhibit 2). We examined whether this decline could be localized to an NIA Division. Analysis of the data revealed that all four divisions funded fewer grants in 2010 than in 2007, although DAB and DBSR showed an increase in 2009 relative to 2008 (Exhibit 8). DAB and DGCG funded roughly the same number of grants in 2010 as in 2004; for DN and DBSR the number of grants for that period increased by 5 and by 8, respectively.

Exhibit 8. Distribution of NIA R21 grants by Division by year, 2004-2010.



Data Source: QVR

Comparison of NIA R21 program to other NIH Institutes and Centers

All NIH ICs use R21 grant mechanism, although not all participate in the parent announcement. Based on the data in the Reporter database, in the past 10 years NIMHD funded the lowest and

NIAID the highest number of R21 grants and NIA was in the top 50% of all ICs (Exhibits 9A and 9B).

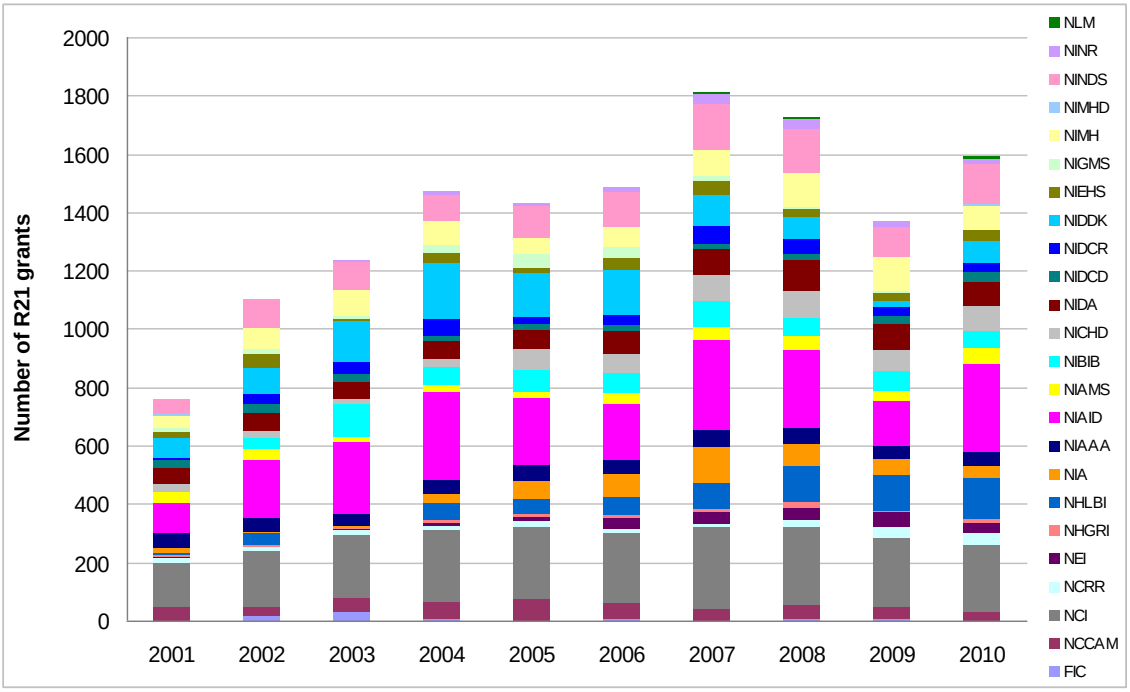
Exhibit 9A. Number of R21 grants by NIH IC, 2001-2010.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total
NIMHD	2						2			11	**15**
NLM							6	7	3	7	**23**
FIC		15	30	5		3	1	6	3	2	**65**
NHGRI	3	3	5	12	10	12	11	20	10	17	**103**
NINR	1	1	6	8	13	16	36	32	17	15	**145**
NIGMS	13	16	13	29	43	41	25	12	6	2	**200**
NCRR	16	14	17	16	18	18	13	22	37	40	**211**
NEI	4	3	3	9	15	34	40	40	48	33	**229**
NIDCD	25	29	22	21	19	21	21	20	26	35	**239**
NIEHS	22	50	4	36	22	38	41	23	28	35	**299**
NIAMS	42	40	21	24	20	38	46	47	37	54	**369**
NIDCR	13	37	44	53	28	34	59	51	29	30	**378**
NCCAM	48	33	45	62	74	58	41	50	42	31	**484**
NIAAA	47	48	38	48	55	48	61	56	42	49	**492**
NIA	16	6	7	33	59	81	120	76	56	42	**496**
NICHD	23	26	19	25	67	66	90	91	71	90	**568**
NIBIB		34	111	63	77	68	87	62	66	55	**623**
NHLBI	12	39	2	55	53	61	91	125	121	137	**696**
NIDA	57	62	61	61	69	76	90	109	89	79	**753**
NIMH	44	73	88	80	60	69	83	115	117	80	**809**
NIDDK	64	88	141	194	145	156	109	77	23	79	**1076**
NINDS	52	93	98	93	103	120	156	152	105	138	**1110**
NIAID	103	198	243	302	232	191	306	266	156	301	**2298**

Data Source: RePORTER

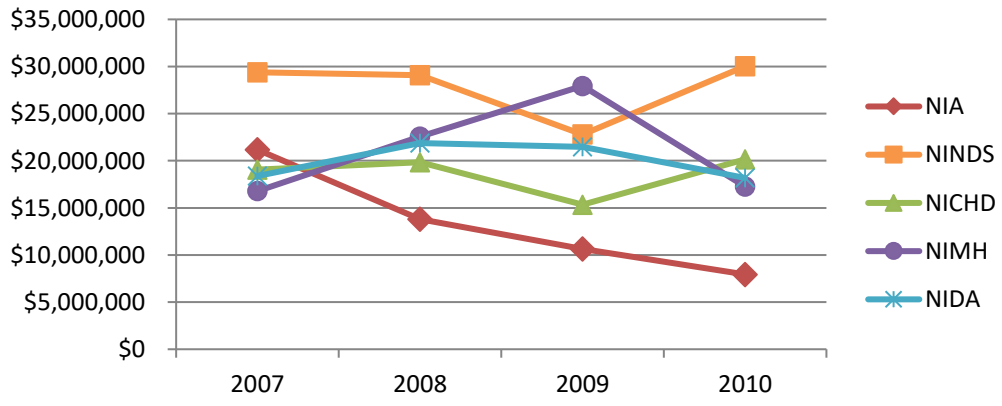
In 2007 – NIA's peak year for R21 awards – the Institute awarded the third largest number of R21s across NIH. By 2010, NIA had dropped to the 11th largest number.

Exhibit 9B. Number of R21 grants by NIH IC, 2001-2010.



We then examined whether the decline in R21 funding observed for NIA occurred at other NIH institutes. As a comparison for NIA, we chose four other institutes with similar total budgets: NINDS, NICHD, NIMH, and NIDA.[9] Exhibit 10 shows that none of the four institutes experienced the same level of decline in R21 budgets as NIA: while NIA expenditures were similar to NICHD, NIMH, and NIDA in 2007, in 2010 the NIA R21 budget was 2.5 times lower than that for these three institutes.

Exhibit 10. R21 funding trends at four ICs with similar total budgets to NIA.



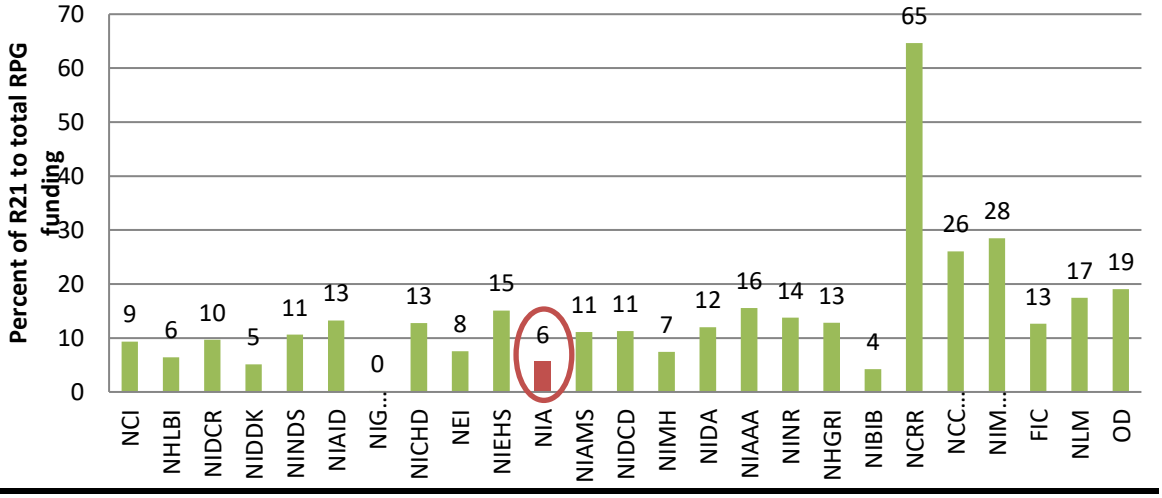
Data Source: RePORTER

Because the total research budget varies widely by institute, we also examined R21 expenditures relative to total extramural research funding in FY2010. This analysis puts NIA at

[9] For FY2010: NIA ($1,109,800K); NINDS ($1,635,721K), NICHD ($1,329,027K), NIMH ($1,489,792K), and NIDA ($1,059,446K). The NIH Almanac (http://www.nih.gov/about/almanac/appropriations/part2.htm)

the bottom of the NIH list. Only three institutes – NIGMS, NIBIB, and NIDDK – spent a lower percent of their budgets on R21s than NIA relative to all research project grant expenditures (Exhibit 11).

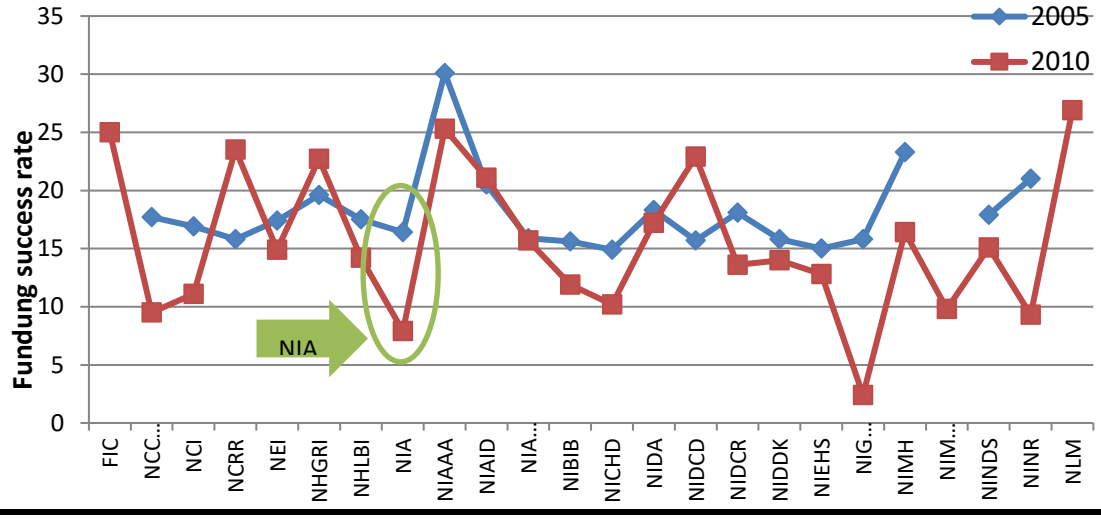
Exhibit 11. R21 funding relative to RPG line for all ICs in 2010.



Data Source: RePORTER

We also compared success rates for R21 grants at NIA with other NIH institutes for two years, 2005, the year before the decline, and 2010. Data analysis showed that while funding success rate for R21 at NIA was similar to most other institutes in 2005, in 2010 NIA had second to lowest success rate of 7.9% (Exhibit 12).

Exhibit 12. R21 success rates at all NIH ICs in 2005 and 2010.



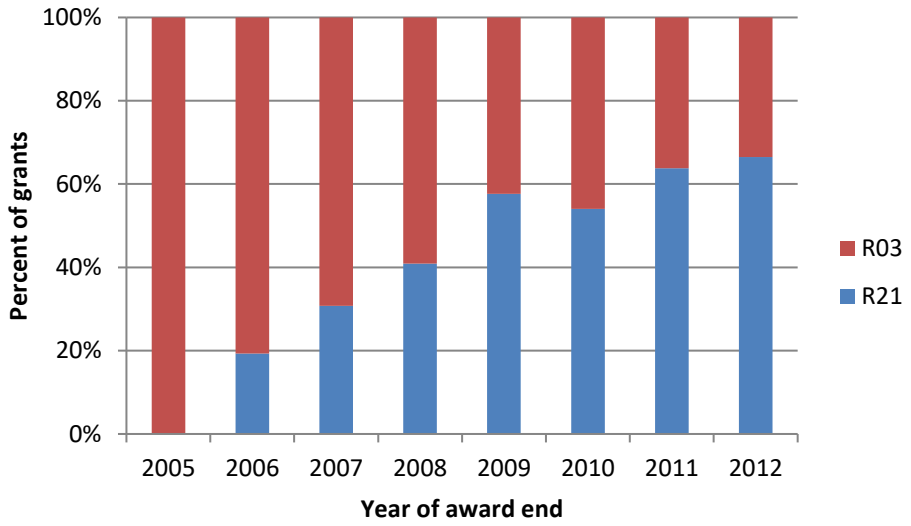
Data Source: RePORTER

Research productivity

We used traditional bibliometric indicators to measure scientific outputs for R21 grants, including number of publications, impact factors, and citation counts. R03 grants were used as a comparator for each of these measures. To examine research productivity for these two funding mechanisms, we compiled the list of R21 and R03 grants awarded by NIA between 2004 and 2010. We queried the eSPA database on each grant funded during this period to obtain bibliometric indicators. Note that the distribution of R21 and R03 awards by program area is different: DBSR awarded most R03s, while DN awarded most R21s (Exhibit 7). Thus, some of the observed differences in productivity might relate to the diversity in the scientific areas supported by the NIA divisions.

Since the number of publications and citations increases with time, older grants are more likely to have higher productivity indicators. In order to determine whether our sample will be vulnerable to this bias, we examined the distribution of grants by year of award end for both the R21 and R03 sets. We found that the R03 set was older than the R21 set, and would be expected to yield more publications and citations, with all else being equal (Exhibit 13).

Exhibit 13. Distribution of R03 and R21 grants by year of award end, 2004-2010.



Data Source: QVR

Our samples included 514 R21 and 325 R03 grants (Exhibit 14). In total, these grants produced 811 and 450 publications, respectively, with the ratios of 1.58 publications per R21 grant and 1.38 publications per R03 grant. The number of publications per $1 million of funding was twofold higher for R03 grants than for R21s (30.8 versus 15.2), although some of the differences may be due to the older "age" of the R03s.

Exhibit 14. Relative grant outcomes for R03 and R21 grants at NIA

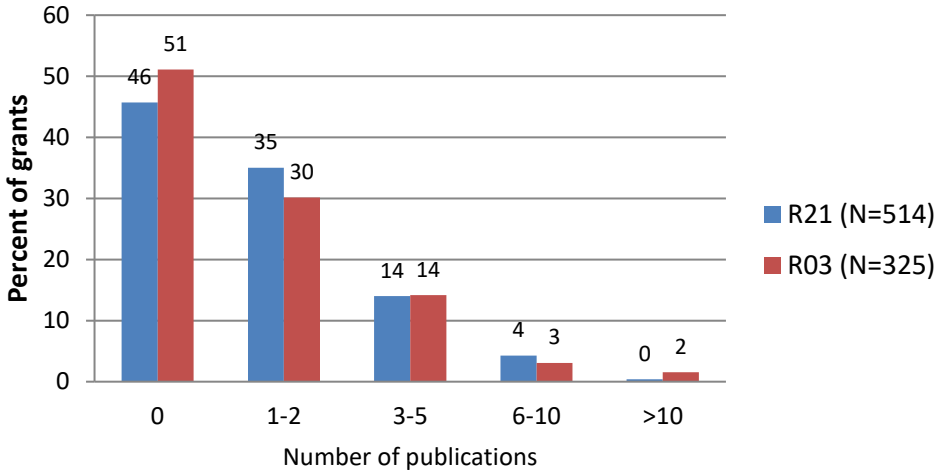
	R21	R03
Number of grants in sample, 2004-2010	514[a]	325[a]

Number of publications, 2004-2010	811[b]	450[b]
Number of publications per grant	1.58	1.38
Total funding, 2004-2010	$82,765,648[c]	$20,468,330[c]
Number of grants per $1 million of funding	9.8	22
Number of publications per $1 million of funding	15.2	30.8

Data Source: QVR (a), eSPA (b), RePORTER (c)

Other bibliometric indicators were similar between the two mechanisms. Exhibit 15 shows percentage of grants with 0, 1-2, 3-5, 6-10, and more than 10 publications, which we used as a measure of productivity. For both programs, we found that approximately half of all grants did not result in a publication, and a third resulted in 1-2 publications, so 80% of all grants yielded up to two papers. Only a small percentage of grants produced more than 5 articles (a total of 27 R21 grants and 15 R03 grants, data not shown). It should be noted that the intent of both funding mechanisms is to support exploratory research and, therefore, the number of publications is expected to be low if the mechanism has been implemented as designed. In addition, the funding period examined, 2004-2010, is relatively recent and presumably the grants will continue to yield publications in the future.

Exhibit 15. Number of publications per grant, 2004-2010.



Data Source: eSPA

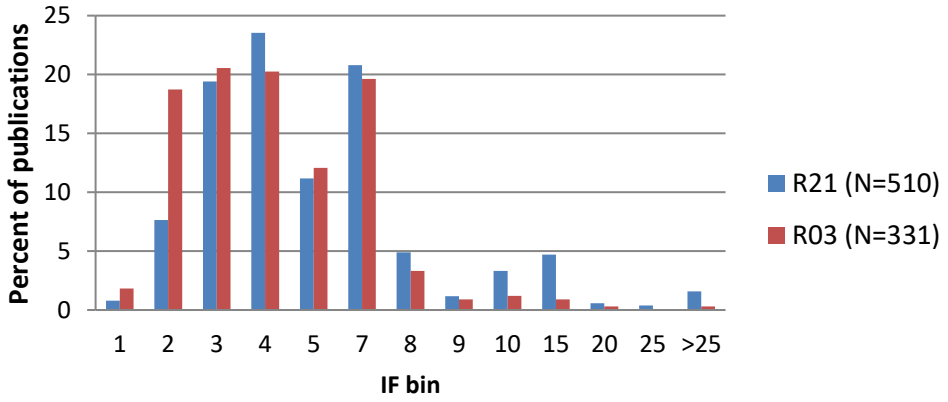
Journal Impact Factor (IF) is routinely used as a measure of journal quality. For reference, note that 82% of journals have IFs that range from 0 to 2.5 and virtually all journals fall in the range of 0-5.[10] Because of this skewed distribution, an Impact Factor of 4.3 places a journal in the top 25% of all biomedical journals.

We examined Impact Factors for the publications resulting from R21 and R03 grants (Exhibit 16) and found that the distribution of IFs was similar for the two mechanisms, with grantees in both programs publishing in high quality journals. The average IF for R21 grants was higher, however,

[10] Stephen J. Bensman. Distributional Differences of the Impact Factor in the Sciences Versus the Social Sciences: An Analysis of the Probabilistic Structure of the 2005 Journal Citation Reports. *Journal of the American Society for Information Science and Technology.* July 2008.

at 5.2 versus 3.9 for R03s (data not shown). This average IF for R21 grants is even higher that the average IF for P01s which was determined to be 4.38 from a previous evaluation of P01s at NIA (data not shown). There is some reason to expect a higher IF for R21 awards because they are high-risk projects.

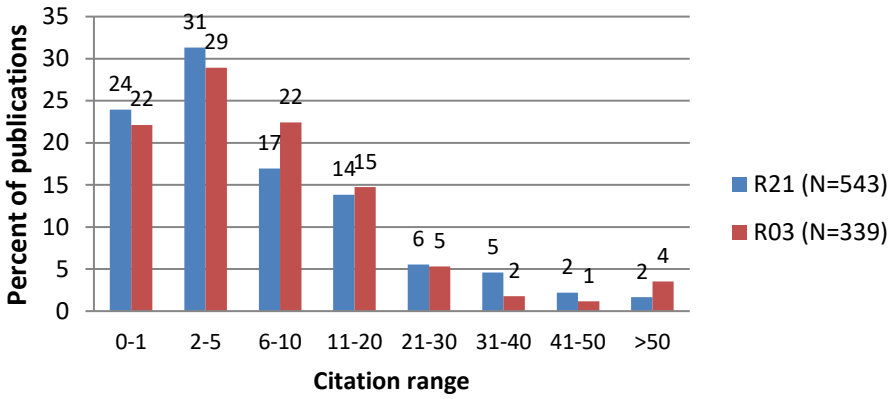
Exhibit 16. Distribution of journals by Impact Factor, 2004-2010.



Data Source: eSPA
IF bin indicates a range of values. For example, the first bin includes all the journals with IF of >0 but <1, the second bin includes all the journals with IF>1 but <2, and so on.

A high number of citations for an article is generally interpreted as evidence of impact on the research community, although citation statistics can be misleading (for example, an article that contains an error may be widely cited). We examined all publications resulting from R21 and R03 grants for citation patterns (Exhibit 17). It emerged that about a quarter of the articles had 0-1 citations and approximately the same percentage had more than 10 citations (self-citations were excluded from the count). Four percent of R21s and 5% of R03s had 40 or more citations per article. The average number of citations was very similar between the mechanisms, at 10.4 for R21s compared to 10.9 for R03s (data not shown). It is worth mentioning here again that because R03 awards on average are older than R21 awards, it is expected that they would have more citations than R21 awards. Exhibit 17 is not adjusted for year of publication.

Exhibit 17. Distribution of articles by number of citations, 2004-2010.



Data Source: eSPA

Follow-up funding

As mentioned in the introduction, the R21 mechanism has come to be viewed by the research community as a stepping stone to obtaining an R01 grant. We examined how many R21s PIs received any additional funding from any NIH institute between 2004 and 2010 (the same funding period for R21s in our sample). We found that a total of 519 awards across NIH of any kind were made to 285 of the R21 PIs in our sample (Exhibit 18A). As there were 514 R21 PIs in our sample, approximately 55% of researchers in this group obtained additional funding from NIH (285/514=0.55). Note that the distribution of grants among PIs was uneven, with some R21 grantees receiving several additional grants, while others receiving no other funding.

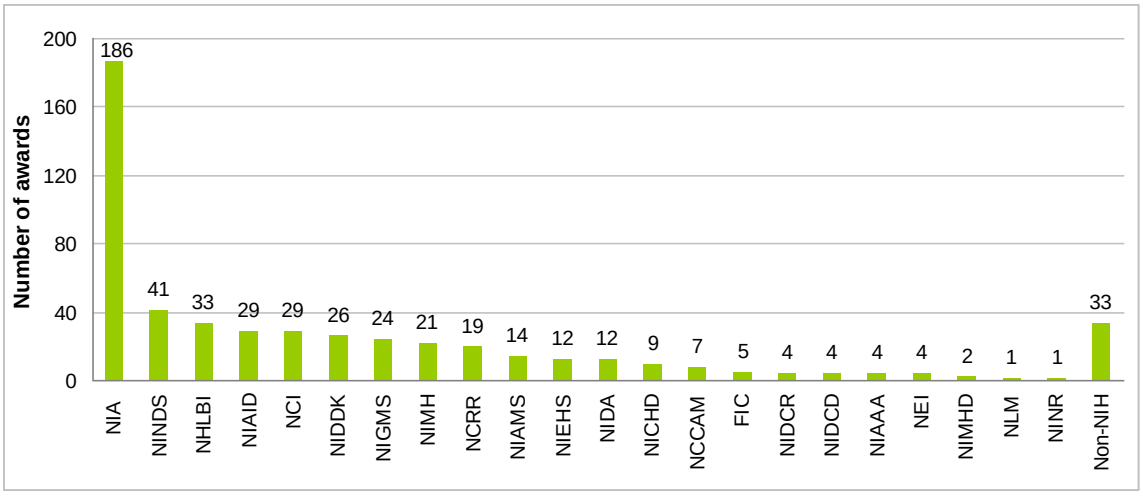
We observed that R01s were the most common additional award among the R21 grantees, with 190 PIs receiving a total of 235 R01 grants meaning that 37% were successful at obtaining R01s (190/514=0.37, Exhibit 18A). We then examined the funding IC for all additional grants received by R21 PIs and found that 36% of these grants were funded by NIA. NINDS came a distant second with 8% (Exhibit 18B).

Exhibit 18. Additional funding sources of NIA R21 grantees.

A. Summary statistics

	Number	Percent of all PIs
PIs in the NIA sample (2004-2010)	514	100%
Additional grants awarded across NIH (2004-2011)	519	N/A
NIA PIs awarded any grant across NIH	285	55%
NIA PIs awarded R01s across NIH	190	37%
Additional Grants awarded by NIA	186	36%

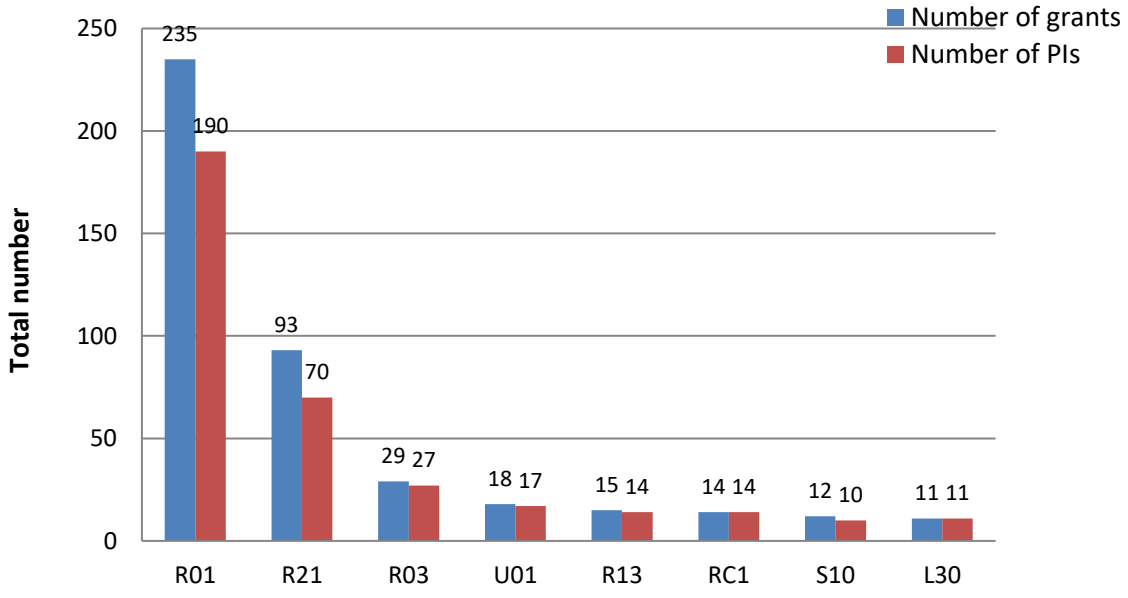
B. Funding by awarding IC



Data Source: QVR

R21 grantees received more than 40 different types of awards, and only the top 8 are shown in Exhibit 19. Among the NIA R21 grantees were the recipients of several prestigious NIH awards, including Challenge Grants (N=14), Young Innovator Awards (N=3), and a Pioneer Award (N=1, data not shown).

Exhibit 19. Other funding rates for R21 grantees, 2004-2010.

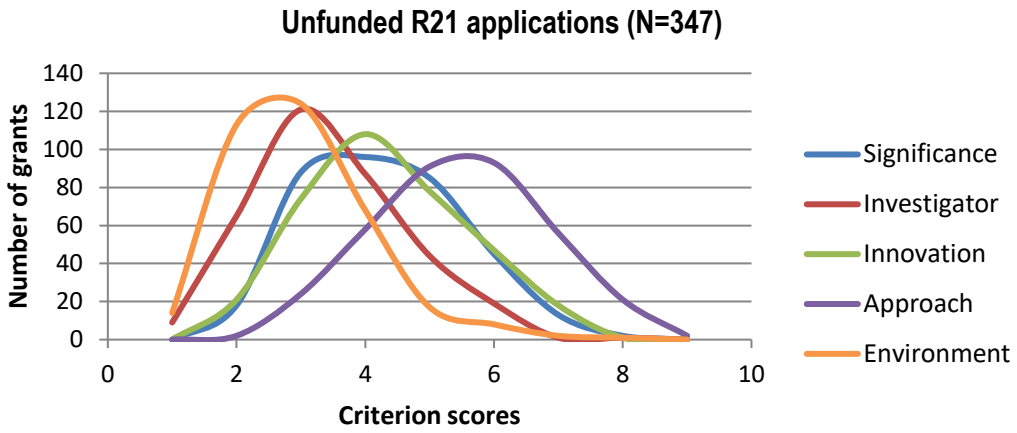


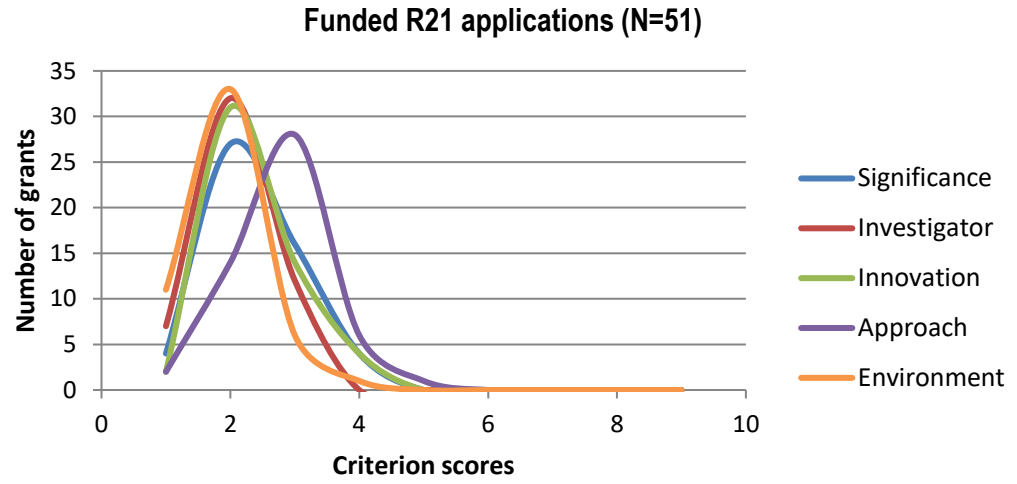
Data Source: QVR
Only 8 mechanisms with the largest number of grants are shown.

Scoring of R21 grants

The stated goal of R21 grants is to provide funding for exploratory, innovative research. To investigate whether study sections placed special emphasis on innovation, we examined the differences in criterion scores for funded and unfunded R21 applications. For this analysis, we only used data for FY2010, as NIH changed its scoring system from 1-5 to 1-9 sometime in 2009 and we wanted to avoid recalibrating the scores for early years. As expected, the average scores for funded applications were significantly better (lower numbers) for each criterion score (Exhibit 20). The largest difference in average scores between funded and unfunded applicants was for approach, 2.71 points or 53%, with innovation following and tied with significance, at 1.9 points or 47% (Exhibit 20).

Exhibit 20. Criterion scores for funded and unfunded R21s, FY2010.





	Significance	Investigator	Innovation	Approach	Environment
Unfunded (N=347)	3.96	3.12	4.00	5.15	2.67
Funded (N=51)	2.08	1.82	2.11	2.43	1.63
Numerical difference	1.88	1.29	1.90	2.71	1.04
Percent difference	47	41	47	53	39

Data Source: QVR
Criterion scores were only available for 51 funded R21s in 2010.

Conclusions

Over the course of the past few years, some NIH institutes began to re-assess the utility of the R21 funding mechanism and consequently, five ICs withdrew from the parent announcement and several others have been making programmatic changes. This past August, NHLBI announced that it will no longer participate in the parent R21 program, citing the internal study that showed that application success rates for R21 were 50% lower for junior compared to established investigators, while the success rates were similar among these groups for R01 grant applications. One issue with the NHLBI study is that it did not consider the costs of R01 versus

R21 awards to NIH when estimating each mechanism's value. Because the costs of R01s are 5.5 times higher than the costs of R21s ($1.5 million compared to $275,000, respectively), the R21 mechanism remains the most cost-effective mechanism to support junior investigators, even with the discrepancy in success rates. It is also possible that differences in success rates between R01s and R21s are probably discipline-specific and that ICs do not consistently represent R21s as a funding mechanism for junior investigators, but rather emphasize innovativeness of the proposal as an important selection criterion. Consequently, five ICs withdrew from the parent announcement and several others have been making programmatic changes.

We examined various characteristics of R21s at NIA and compared them to the R03 and R01 portfolios. In addition, we compared NIA R21s to R21s at other ICs using a variety of indicators. We found that the number of and funding for R21 grants began to decline after 2007 and continued to decline over the course of the next four years (Exhibits 2-3). The number of R03s and R01s also declined over this period, but not nearly as dramatically: the relative decrease was 63% for R21s, 44% for R03s, and 2.4% for R01s. Funding as a percent of the RPG line and success rates also declined for all three mechanisms. We also found that the number of applications remained relatively stable: it declined by 11% compared to the 63% drop in the number of awards.

Most R21s between 2004 and 2010 were awarded by NIA to research universities with very high research activity as determined by the Carnegie classification. CA, NY, MA, TX, and IL were the top five states receiving the grants (data not shown). Approximately 60% of R21s at NIA were awarded through parent announcement and 40% through RFAs (Exhibit 6). Within the Institute, the Division of Neuroscience awarded the highest number of R21s, and the Division of Behavioral and Social Research awarded the highest number of R03s. The decline in the number of R21s from 2007 to 2010 occurred at all Divisions (Exhibits 7-8).

Our investigation of R21s at other ICs revealed that, in contrast to NIA, funding levels for this mechanism at four other institutes with similar budgets did not decline. In 2010, R21 funding at NIA relative to RPG was one of the lowest at NIH. Similarly, funding success rate for R21s at NIA was lower than at most other institutes. This was in contrast to 2005, when NIA had a success rate that was similar to most other ICs (Exhibits 10-12).

We examined various indicators of research productivity and compared them between R21s and R03s (Exhibits 13-17). We found that the number of publications per grant was similar between the two mechanisms, but because R03 funding is significantly lower than R21 funding, the number of publications per $1 million of funding was twice as high for R03s (30 versus 15 publications). Note that R03 grants were somewhat older than R21 grants, which probably contributed to the apparent higher productivity of R03s. However, R21 grantees appeared to publish in higher quality journals based on Impact Factors. Average number of citations to research articles published by grantees was similar between R03s and R21s. We found that 55% of R21 grantees received other funding from NIH, including prestigious and highly competitive cross-NIH awards. NIA emerged as the most frequent funder of other awards received by R21 grantees as follow-on awards.

The R21 funding mechanism was designed to provide funding for innovative, potentially high impact projects. We investigated whether the innovation criterion for R21 grantees was better

(lower) than four other criteria (significance, investigator, approach, and environment) and whether the differences in the scores for funded and unfunded applications were larger for the innovation criterion (Exhibit 20). Examination of score data revealed only small differences among the five criterion scores for successful applicants. Approach rather than innovativeness of the proposal appeared to be one of the more determining factors in the success or failure to obtain an R21 grant.

NIA division staff who reviewed this report suggested several possible reasons for the decline in R21s that began after 2007. One of the proposed reasons was related to the change in how study sections review applications from new/early stage (NI/ESI) versus established investigators. In the new review process, proposals from NI/ESIs are considered separately, in order to give younger researchers a fair advantage over their established peers. This "special treatment" only applies to R01 proposals, and as a result may have tempered the enthusiasm among junior investigators for R21 funding. This hypothesis predicts the decline in the total number of applications, both at NIA and at other ICs. However, we observed that the number of applications remained relatively stable and that most of the decline could be attributed to an increase in the competitiveness of the R21 program (Exhibits 2-5). In addition, NIA staff independently examined the possibility that NI and ESI investigators were deterred from applying for R21s, and found no evidence to support this idea (data not shown).

Another suggestion from NIA was that the study sections apply the same evaluation criteria to R21 proposals as to R01s, and so few R21s get funded because these proposals are less mature and more uncertain. Our data suggest that, in fact, success rate for R21 steadily declined over time (Exhibit 5). On the other hand, this downward trend should have been seen at other ICs, since study sections review the proposals regardless of the institute assignment. We found no decline at four other institutes examined.

NIA staff also proposed that when the Institute transitioned from division-specific to NIA-wide budget, the change may have increased the pressure on the staff to use discretionary funds to pay larger grants, at the expense of R21s. We do not have the data to support or dispute this hypothesis.

Another argument put forth was that the decline in R21s might be due to the decrease in the number of FOAs that use this mechanism. We examined this possibility and found that the number of funded grants and success rates declined similarly for parent announcements and FOAs (data not shown). Finally, the suggestion was made that changes in the length of applications may have had an effect on the R21 mechanism. We think that this is unlikely because (a) the NIH began accepting shorter applications in 2010, after the decline took place and (b) the decline was not observed at four other ICs.

In conclusion, we found that most of the decline in the number of R21s which began in 2008 was due to lower success rates. We could not determine whether the application pool became weaker, or if reviewers began applying tougher standards to R21 applications, or if the observed decline was simply temporary and the number of applications will rebound within the next few years. We believe that R21 at NIA is a productive program, which improves the chances of obtaining follow-up funding at NIH.