

Grant Writing

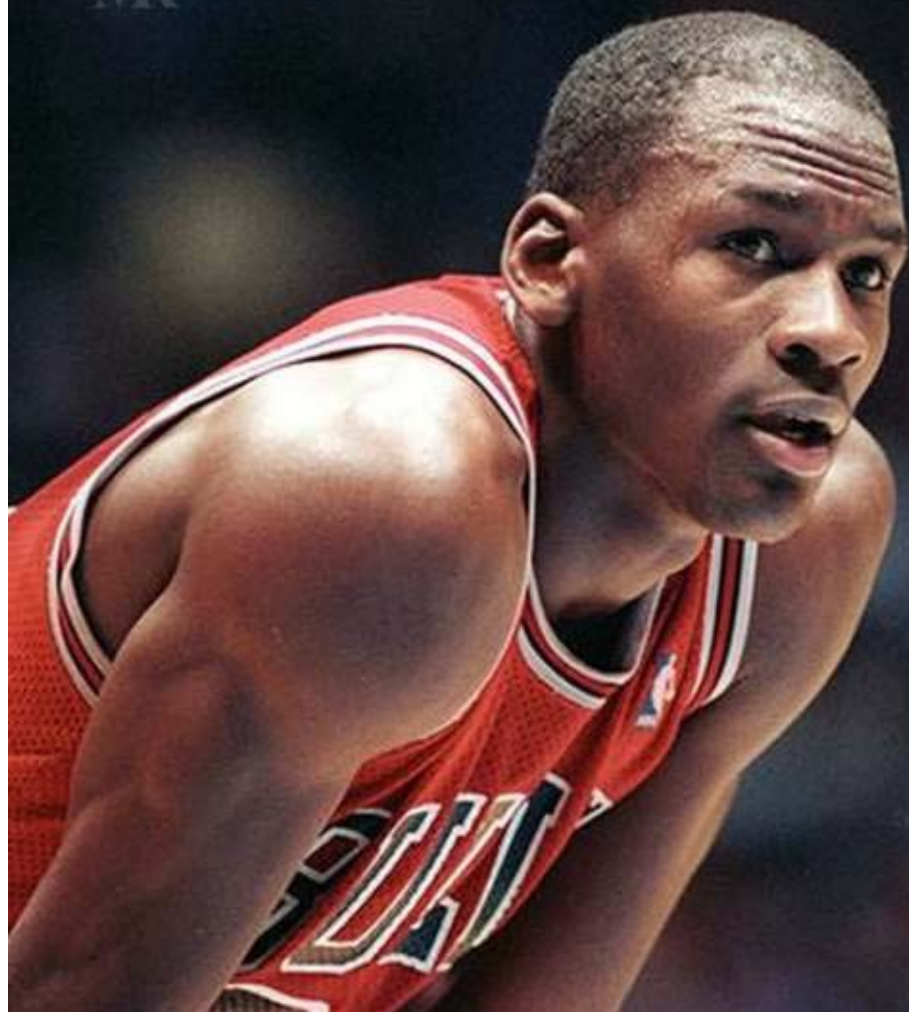
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“Many receive advice, only the wise profit from it” – Harper Lee

- There are many ‘grant writing’ courses many of which are based on ‘successful grants’.
- Such successful grants share certain common terms, design features and styles
 - This presentation won’t review those formulaic versions of grant writing specifically but will focus on how to design studies and then how to communicate essential elements clearly



MR



I've missed more than 9000 shots in my career. I've lost almost 300 games. 26 times, I've been trusted to take the game-winning shot and missed. I've failed over and over and over again in my life. And that is why I succeed.

”

What are the worst ways to write a grant?

- “I really need a grant to be successful!”
- “My chairman says that they won’t protect my time forever. I HAVE TO GET FUNDED!”
- “I won’t be an independent investigator until I have an R01!”
- “If I don’t have two R01s, I won’t make tenure!”
- “There’s \$500,000 per year for five years. That’s \$2.5 million dollars...how should I spend money on science?”
- “That jerk is higher on the NIH funding ranking than me? I’ve got to beat them!”
- “No one will ever fund me to do something really big, that’s out of my reach. I should stay within these safe boundaries...”

Rule number 1

- ALWAYS think about the best science
 - As opposed to:
 - No one will fund me for the best science but this is something “safe”
 - Others were successful doing ___ so I should do that
 - This RFA has \$50,000 per year for 5 years; how should I spend that money?

Example

- RNA-sequencing of leukocytes gives the gene expression pattern of those cells
- Let's do an RNA-seq in ICH!

- Well....that doesn't START with the best science you can think of. Why do this?
- Well, we know that ICH causes a marked serum inflammatory response but so would any major medical event. Is there reason to believe that this is anything but demargination?
- We could look at the WBC differential and see if there is any part of it that is independent of the severity of the ICH itself

- Therefore, the 'best science' would be to first see if the leukocytes make a difference in outcomes independent of the severity of ICH itself

Example

- IVH is bad, we have a cool device to remove IVH, let's remove it!
- Well, not ALL IVH is bad. Some IVH probably doesn't do anything. We need to have some criteria for who we'll remove the IVH in. We don't want to do more harm than good.
- And, is the 'damage' already done and removing the IVH wouldn't reverse it?

- Basically, whatever idea you have could probably be better than when you first thought of it.
 - Be ready to jettison an idea with a fatal flaw
 - Be ready to modify and improve and perfect from your original design
 - Be ready to find collaborators with the expertise you need to accomplish the best science you can

The Scientific Method

- Observation
- Question
- Hypothesis
- Predict based on the Hypothesis
- Test
- Iterate to new Hypotheses

The Scientific Method

- Observation
 - Observational studies include case series, case-control, surveys, cohort studies
 - May also be a literature review
 - Observational studies or data build the foundation for most research.

The Scientific Method

- Questions:
 - Any number of questions may be asked but it's important in research to understand that these questions should be:
 - Novel or needs additional evidence
 - Consider having a conceptual model that explains the observation
 - Starts with observations, best if you can cite it
 - For example: If women have more aneurysms than men, how are women different from men? Is it estrogen? Is it uterine? Is it vascular? Is it height? Is it weight? Is it pregnancy related or menopausal related or progesterone related?

The Scientific Method

- Hypotheses:
 - A hypothesis is a testable explanation of the observed phenomenon
 - “If ___ is true, then ___ should happen” is a VERY strong testable explanation or hypothesis
- Some common errors:
 - Statements – A statement may have an implied question it but usually best to clarify into a question. “Women are more likely to have aneurysm than men because they have a higher estrogen burden” is a statement with an implied hypothesis.
 - Try: If higher estrogen burden is a higher risk of aneurysm, then women with low estrogen burden will have lower occurrence of aneurysm than those with higher estrogen burden”
 - Too many hypotheses in the hypothesis: “We will test the hypothesis that women are more likely to have aneurysms because of higher estrogen burden over time in pre and post-menopausal states compared to men and burden of hormones including progesterone and testosterone.”
 - Too few considerations in the hypothesis: In the above example, what about progesterone? What about surgery? What about age of menarche or surgical menopause or use of hormone replacement therapy?” All of these can be added into the hypothesis but still be part of the overarching hypothesis unlike the prior example where each item was a different hypothesis.

What's a specific aim?



- What will be the scientific achievement or advance that the study will achieve? What are you specifically trying to accomplish?
- Typically a 'task' is not a specific aim unless the task is so large it is of itself a major accomplishment
- Determine, establish, identify are common scientific aims
- How will your work advance the field?
- "So what?" if the study is positive or negative

Some examples

- Specific Aim 1: We will recruit 200 cases of aneurysm in women and men.
 - This isn't really a scientific aim, it's a task!
- Specific Aim 1: We will test the hypothesis that higher estrogen burden is associated with higher risk of aneurysm formation.
 - This is a hypothesis, not an aim!
- Specific Aim 1: Through these experiments, we will establish if higher estrogen is associated with aneurysm formation independent of all other risk factors.

On Reviewers

- Learn why you fail
 - If only the reviewer had read my grant
 - If only I had a reviewer who understood what I was doing
 - If only the reviewer _____

How to design a grant

- Prior to but also during the writing of a grant, one is 'designing the grant'
- You are seeking to put forth the 'best possible science' that you can think of.
- What is the 'best science'?
 - It's typically judged on it's impact into the field which can be further scaled into:
 - Significance: Who cares? Does it impact a lot of people? Does it make a big leap forward to a small group of people?
 - Innovation: Haven't we done this already? Is this a minor iteration of prior work? Is there a technical innovation?
 - People: Are *you* and your team the right people to do this, even if it's a great idea?
 - Methods: Is the method you are using well powered, internally and externally valid, robust and reproducible?

What isn't the 'best science'?

- Hm, this RFA is for \$50,000 per year for 5 years...how shall I spend this money?
- I've proven this thing and I want to prove it again
- They'll never fund me to do ___ so instead I'll do this thing that they will fund me to do
- Please fund me!

Solve this problem

- Solve this problem: Women are less likely to have all subtypes of stroke EXCEPT intracranial aneurysm related subarachnoid hemorrhage (SAH) where they have a higher rate of SAH than men.
- Some 'x' factor is related to why women are more likely to have aneurysmal SAH than men.
- Solve for X

- Women smoke less and have less hypertension than men yet hypertension and smoking are the greatest risk factors for aneurysmal SAH
- Solve for X

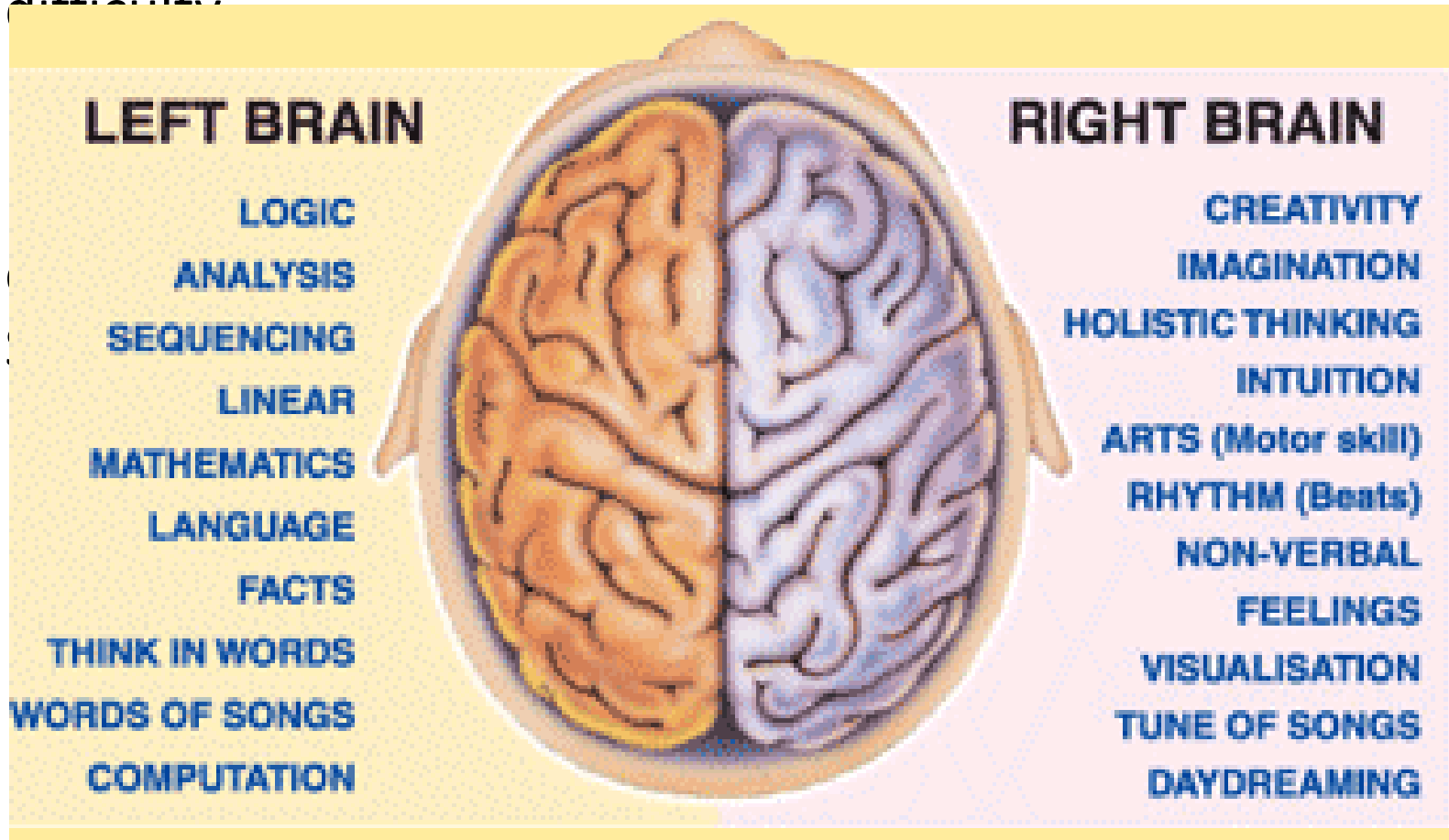
- Women are also shorter than men, have more estrogen, less androgen/testosterone, different body habitus, have two X chromosomes,
- Solve for X

Solve this problem

- Hopefully you generated some interesting hypotheses as to why there is a gender difference to SAH compared to others.
- Now solve this problem:
- What's my next grant idea?....
- Solve for X

Vapor Locked?...

- Given a task with a defined set of instructions and education, most scientists will be successful without much difficulty.



Big Picture and Detail Oriented

- I have often said that there are three types of successful people in academics
 - Big picture – The person who can see the forest for the trees, make connections between disparate ideas and concepts and facts, grand vision
 - Detail oriented – Methodical detail oriented individual who can master hundreds of moving parts, remember minute detail, rules, facts, figures, handle enormous complexity and detail
 - And the most successful is the person who can do both
- If one considers right brain to be the big picture brain and the left brain to be the detail oriented, then first know which you are. Are you detail oriented, big picture, or both?
 - Practice DEFINITELY alters your brain and pathways. You can ‘think’ a different way by practicing that way of thinking
 - Most rote, scientific learning is very left brain oriented. Memorization and implementation without mistakes of specific logical, rational pathways and concepts. Detail oriented
 - But some actually teach conceptual model building, intuitive thinking, getting the ‘sense’ of something or the ‘feel’ of something.

Three major types of new grants

- Next logical step
- Same technique, different phenotype
- Inspiration!

Next Logical Step

- This follows a particular line of research starting with an over-arching hypothesis.
 - Remember, hypotheses are strongest when they begin with an observation that is strong/reliable
 - This doesn't have to be your own line of research although that much stronger if it is.
 - It demonstrates the importance of knowing what it is that you have done and how it fits into the literature.

Determining the next logical step?

- Try to always remember your overarching hypothesis and continue to test until you can confidently
- Obesity is mediated
 - If true, hypothesis degree relatives should have a high environmental exposure
 - If true, hypothesize risk of obesity than and era/age
- Studies demonstrate there is a gene or a : obesity or makes an
 - If true, a genome wide obesity or protection
 - If true, a family-based protection from obesity
- GWAS studies identify association with obesity

Abstract

Until just a few years ago, the genetic determinants of obesity and metabolic syndrome were largely unknown, with the exception of a few forms of monogenic extreme obesity. Since genome-wide association studies (GWAS) became available, large advances have been made. The first single nucleotide polymorphism robustly associated with increased body mass index (BMI) was in 2007 mapped to a gene with for the time unknown function. This gene, now known as fat mass and obesity associated (*FTO*) has been repeatedly replicated in several ethnicities and is affecting obesity by regulating appetite. Since the first report from a GWAS of obesity, an increasing number of markers have been shown to be associated with BMI, other measures of obesity or fat distribution and metabolic syndrome. This systematic review of obesity GWAS will summarize genome-wide significant findings for obesity and metabolic syndrome and briefly give a few suggestions of what is to be expected in the next few years.

Highlights

- GWAS have greatly increased the knowledge about obesity genetics.
- Common forms of obesity are polygenic with small effects sizes of each variant.
- The largest genetic effects size on obesity are reported for *FTO* variants.
- We expect large advances over the coming years regarding knowledge on gene function.

What's the next logical step?

- Evaluate what *FTO* does
 - Animal knockout models?
 - Tissue reporter assay models?
 - RNA inhibitors?
- Find more genes?
 - Larger sample size
 - Rare variant analysis
 - Extreme discordant phenotype

Some

- The 'next logical step' is it. Some bigger, faster, and
- If you happen to be the largest biggest hound or at least
- The next logical step can sometimes lack 'innovation', be boring or uninspiring.
- Try to make substantial steps, not incremental baby steps.
 - If a choice between a minor increment of the same thing
 - Compared to a substantial leap forward, reviewers will choose the leap forward.



Some caveats

- The next logical step with a substantial leap forward may be utilizing a skill set that you don't already have
- Need to learn it, collaborate with those that have it, build teams and yet contribute substantively to the effort.

Same technique, different phenotype

- An innovative technique has worked successfully in phenotype A
- In particular if there is an advantage to the innovative technique and the technique is applicable to a wide variety of conditions
- Unlike the 'next logical step' where the investigator may have to learn a new technique, here an investigator must learn a new phenotype!

Same technique, different phenotype

- Investigators working on blood pressure refractory to medications invent an implant that can detect high blood pressure and then stimulate the carotid sinus to lower blood pressure
- Small randomized trials succeed and the device is getting approval for use in refractory hypertension.
- What other phenotypes could this be tried in?

The electronic implant that could control high blood pressure without drugs

- Monitors the signals sent through a nerve in the neck to regulate blood pressure
- If it detects a high reading, it can overwrite the signal, lowering the pressure without drugs

By MARK PRIGG 

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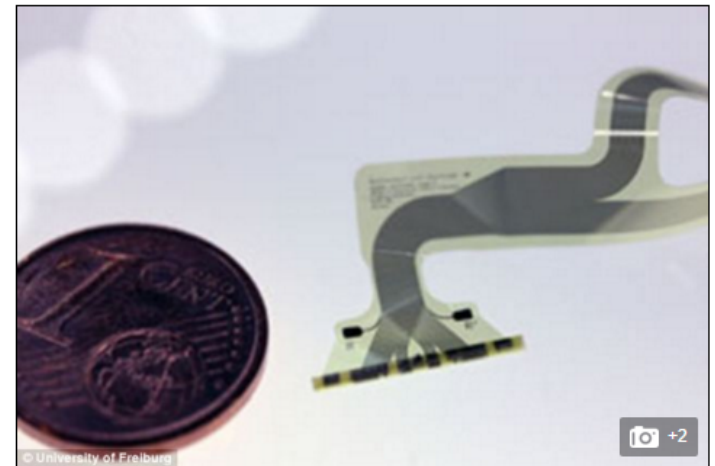


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Researchers have unveiled a tiny implantable patch that can automatically monitor and control the wearer's blood pressure.

The German invention monitors the signals sent through a nerve in the neck to regulate blood pressure.

If it detects a high reading, it can overwrite the message, lowering the pressure without drugs.



© University of Erlangen
The German invention monitors the signals sent through a nerve in the neck to regulate blood pressure. If it detects a high reading, it can overwrite the message, lowering the pressure without drugs.

Same technique, different phenotype

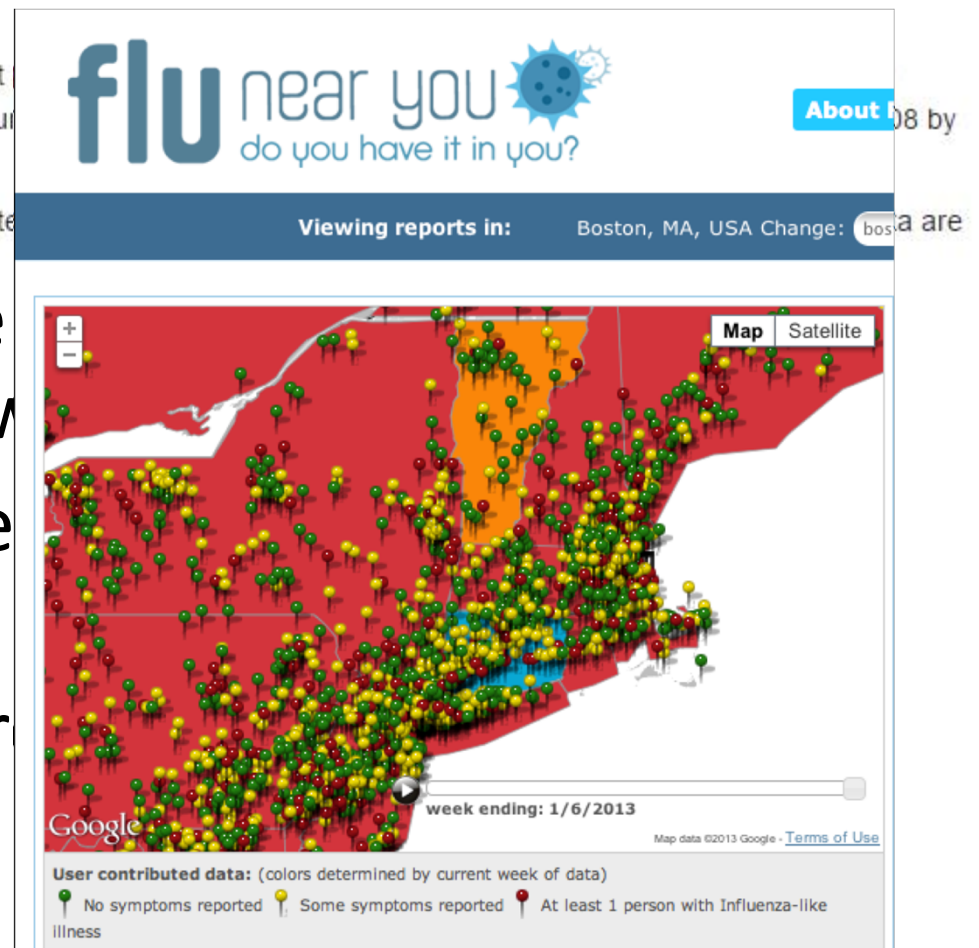
Google Flu Trends

From Wikipedia, the free encyclopedia

Google Flu Trends was a web service operated by Google. It aggregated Google search queries, it attempted to make accurate predictions of flu activity. Google.org to help predict outbreaks of flu.^[1]

Google Flu Trends is now no longer publishing current estimates and is only offered for declared research purposes.^[2]

- epidemic but Google predicted the same epidemic two weeks in advance
- The predictions were 97% accurate!
- Subsequently, it over



Some caveats

- The technique must be relevant and appropriate to the disease in question
 - Gene expression studies have often failed to progress in acute diseases where the disease itself is likely to affect gene expression
 - OR that the only available tissue was leukocytes
- Need to learn/publish in the new phenotype or partner with those that are experts in that field; build collaborations!

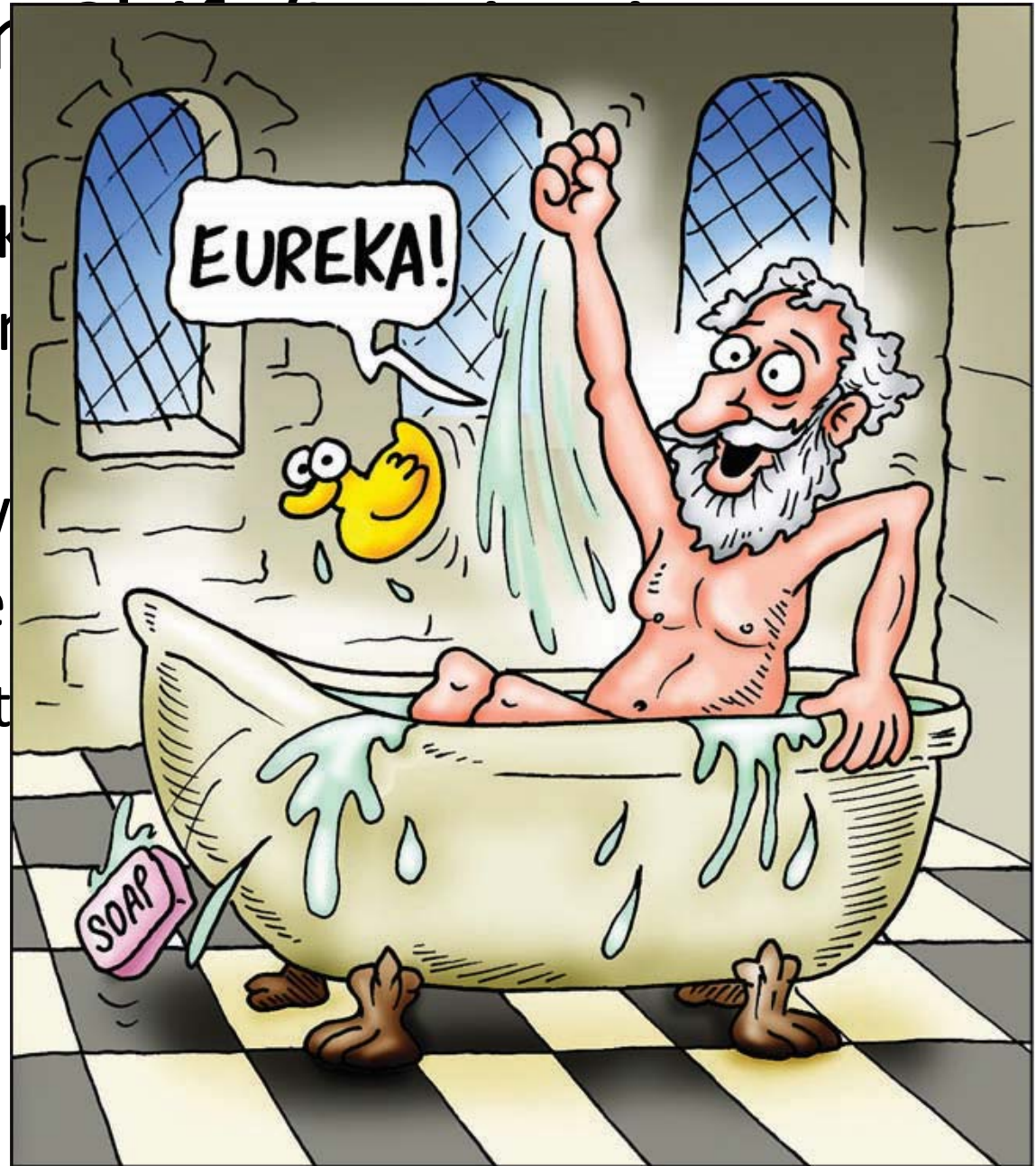
Paradigm Shift/Inspiration

- Hero, king of Sicily, commissioned a new crown to be made all of gold.
- But when he received the crown, he became very suspicious that the crown was not made all of gold but in fact had mixed in some very cheap silver(!)
- The King commissioned Archimedes to find out if it were pure gold WITHOUT ruining the crown but he wanted proof that it was made purely of gold
- Archimedes struggled with the problem for many weeks but then went to take a hot bath
- In it, he had a moment of inspiration when he noticed, as of course, millions of others had, that when he got in the tub, his body displaced a certain volume of water.

- He then developed an experiment.
- First he acquired pure gold and using a scale created a quantity of gold that was the exact weight of the crown
- He filled a tank with water and put the pure gold in. When he removed the gold, he could measure the amount of water that was displaced.
- He then put in the crown. If the crown displaced exactly the same amount of water, then no water would spill over the edges of the tank and it should reach just to the top
- But, he knew that gold was denser than silver and therefore if silver made up the weight of the crown, it would displace MORE water
- Indeed, the crown did displace more water proving that crown was not made of pure gold!

Paradigm

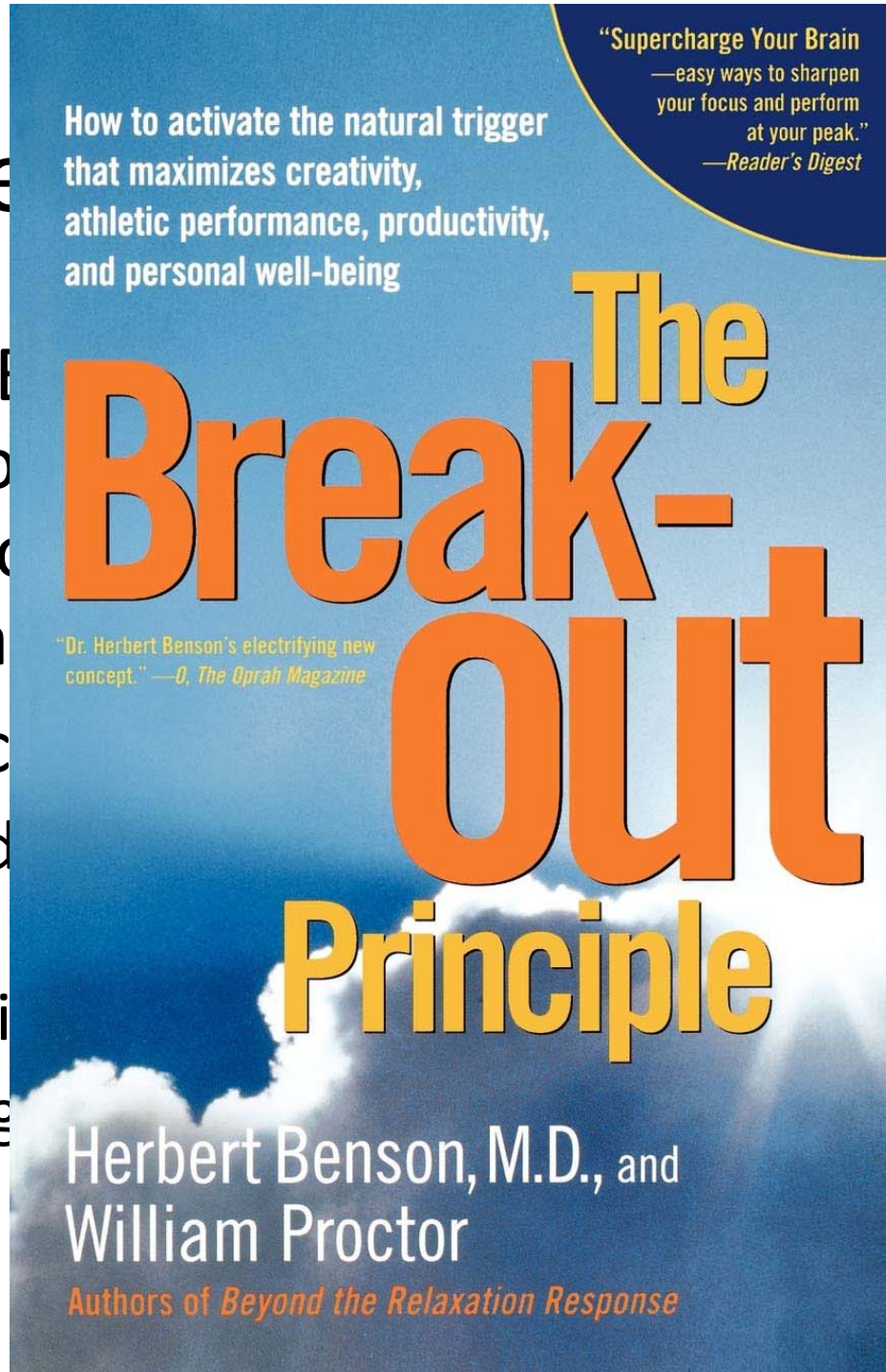
- Archimedes took one that everyone was rising when you that had been w matter had diffe
 - And combined t
 - EUREKA!



Paradigm Shift/Inspiration

- There will DEFINITELY be moments when you will see something, a pattern or a combination of two seemingly disparate facts that you can combine together into a new idea/concept
- PAY ATTENTION! Write them down, investigate and search on these. Sometimes, they are the best of all!

Is there



ration?

- Herbert Benson's Relaxation Response meditation technique
- The Break-out Principle
- Used Arc...
 - Studied a topic
 - Then did
 - Leading

or of the treated that pressure;

breakouts d of time on

ent

Caveats of Inspiration

- Not reliable... 😞
- Sometimes not valid... 😞 😞 😞
- Often not believed!
- Or completely unfeasible

All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident.

Arthur Schopenhauer

Assessing Ideas

- Significance/Impact
 - Look up the number of people affected by the condition
 - Look up the economic burden
 - The rate of mortality
 - Rate of disability
 - Will the science make substantial advancement towards reducing this?

Assessing ideas

- Feasibility
 - Effect size estimate to find differences
 - Ability to sample (human or animal)
 - Technologic factors
 - Cost
- Innovation
 - Always see if it's been done before!
 - Innovative in topic, technology or technique
 - Combining two areas into one idea
 - Novel concept or idea being tested

Assessing Ideas

- Can you do it?
 - Publication record
 - Area of interest
 - Mentorship
 - Support
 - Environment

Some Tips and Tricks

- Innovation: Technical innovation usually ticks this box off. If you don't have one it's still possible but must be assessed that the techniques applied are truly innovative
- Sex as a biologic variable: Really consider how sex may affect the outcomes or analysis. Don't just include as a covariate.
- Age across the spectrum/race/ethnicity: These unalterable traits are definitely a factor. Do you have enough power? Are you considering the effects on different age groups?
- Internal Validity: Are you doing quality control checks; inter-rater reliability, are your measures supported by the literature?
- External Validity: Is your population representative of the target population? Multi-center, academic and community, reflects the target population
- Robust and Unbiased: Is your sample size sufficient and externally valid

Study Design

- Why did you design your study the way you did? This is a place to respond to reviewers before you are reviewed!

D.2. Experimental Design

We propose to perform serial detailed motor, cognitive, and neuroimaging follow-up of 250 ICH cases.

Conceptual model: Figure 4 presents our conceptual model for the potential future risk of cognitive impairment after ICH with the red arrows indicating unknowns to be tested by the current proposal.

Design Considerations:

- 1) **Enrollment/feasibility:** Currently, 163 cases of ICH out of a planned 500 have already been enrolled into the ROSE study. By the proposed starting date, only 78 cases would not be eligible by time for enrollment into ROSE-LAWN, leaving 422 potential cases from which to recruit the planned 250 cases. Based on the past 12 months, we anticipate enrolling 97 cases per year until the target of 500 cases is achieved. The ROSE study was specifically designed to avoid the early mortality rate of ICH of 40-50%.²⁵⁻²⁹ Moribund cases and those made comfort care or hospice represent more than half of the early case-fatality and are not enrolled. Brainstem ICH are excluded given the very high mortality rate and cases have up to 45 days to enroll into the ROSE study. In the previous ERICH study, we found that 93% of cases that survived to 3 months were able to perform their 12-month phone follow-up. However, given the additional challenges of re-enrollment, in-person evaluation and repeat MRI, **we conservatively estimate 60% will be re-enrolled.** The ongoing COVID-19 crisis has led to a cessation of enrollment which we anticipate will occur for approximately 3 months. For the purposes of the current proposal, however, this delay provides additional cases for a longitudinal study and funds in ROSE are being held for restart of recruitment.
- 2) **Centers:** All of the recruiting centers have 3T GE MRI scanners with harmonized protocols undergoing baseline human volunteer and annual quality control scans using a standard phantom. The centers also undergo in-person site initiation and annual site-specific calls to address issues and scanner upgrades.
- 3) **12 to 24-month follow-up window:** Previous published data has identified rate of 19% of patients developing progressive cognitive decline after 6 months with an additional 5.9% per 12 months or 24.9% at 18 months²⁴. Thus, we utilize a 25% rate of progressive cognitive decline at an average of 18 months post ICH for our analyses and sample size calculation. All analyses will be time-adjusted from the date of ICH.
- 4) **Interleukin-8 as a target:** Our preliminary data as well as literature support (C.2.2) finds a key role of monocytes, inflammation and IL-8 expression as well as toll-like receptors (TLR) after ICH. We readily admit that our preliminary data has yet to be confirmed and that a wide milieu of inflammatory changes occurs after ICH. However, IL-8 is the candidate gene with the **strongest preliminary data** but we intend to perform a

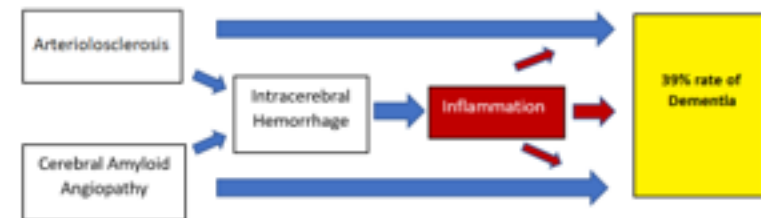


Figure 4. Conceptual Model. The major mechanisms of ICH are cerebral small vessel disease and cerebral amyloid angiopathy. The very high rate of dementia after ICH may be from these mechanisms alone or could be related to progressive neurodegeneration triggered by the ICH itself, such as from inflammation.

- 5) **Intraventricular hemorrhage:** Our prior research has found an important relationship of intraventricular hemorrhage (IVH) with worse outcomes specifically related to incontinence and gait dysfunction. We will include this factor as a variable in analysis but an IVH specific aim was not included as we have no preliminary data to support the relationship and IVH occurs in only 40% of cases (estimated 100 of the 250 cases total of which 25 would have progressive impairment). Future studies may be possible to evaluate this phenomenon.
- 6) **DISCOVERY:** We are excited to be active participants in the recently funded DISCOVERY study which will soon begin recruitment of 8000 cases of stroke including 2000 ICH. **A distinction of our proposal includes RNA sequencing serially** (baseline, 3 months and long-term follow-up) which is not included in DISCOVERY and is a key element of **identifying inflammation after ICH**. We further intend to make our data directly available to our collaborators in DISCOVERY to augment their sample size.

Robust and Unbiased Results

Our study design has incorporated specific features to yield robust and unbiased results detailed here:

- 1) **External Validity:** Population-based study: Incorporated into our study is a population-based collection of cases in the Greater Cincinnati/Northern Kentucky region. The parent study included chart abstraction of all cases in the population (including non-enrolled subjects) and found nearly identical rates of risk factors for our enrolled subjects to non-enrolled subjects with respect to hypertension, hypercholesterolemia, frequent alcohol use and anticoagulant use⁹⁴.
- 2) **Internal Validity:** To develop internal validity, all of Dr. Woo's studies harmonized phenotype definitions including case definition, location of ICH, risk factor definition and study design. All personnel have training and certification on tested parameters for the study and routine comparisons for accuracy will be incorporated. Finally, we incorporate an extensive data-cleaning process which includes input, logic checks, data queries, missing data assessment and phenotype harmonization.
- 3) **Robustness:** The largest DTI in ICH study reported in the literature included 71 cases with only baseline imaging^{39, 40}. The ROSE-LAWN study with 250 cases would represent a markedly robust dataset of serial and long-term neuroimaging and cognitive assessments.
- 4) **Race/ethnicity:** Our studies have had a particular interest in race/ethnic disparities of ICH including that disproportionately affected minority populations have double the incidence rate and are affected 10 years earlier. Under current enrollment in ROSE, 36% of our cases are black but only 5.6% Hispanic. To address this, we have added Columbia University and University of Illinois-Chicago to the study. During the prior ERICH study, Columbia University's ICH enrollment was 45.6% Hispanic, 25.7% black (71.3% minority) and Chicago was 50.3% black and 19.4% Hispanic (69.7% minority).

Chicago was 50.5% black and 13.4% hispanic (63.7% minority).

Sex as a Biologic Variable

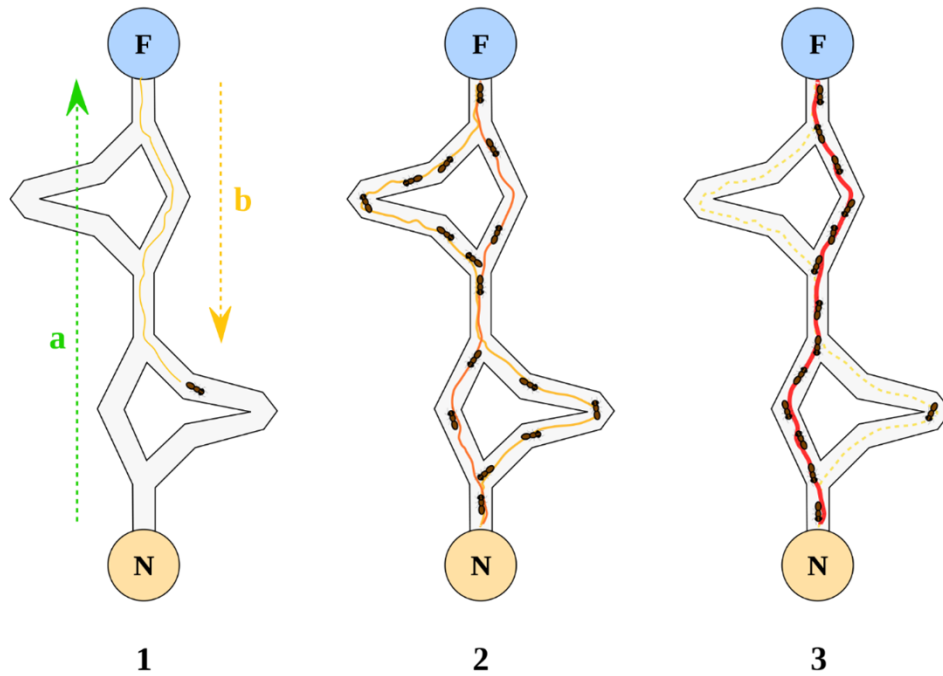
Pre- and post-menopausal status have been found to be predictors of outcome after ischemic stroke and **risk of cognitive decline**.^{95, 96} Putatively, estrogen may be neuroprotective according to preliminary animal and clinical studies.⁹⁷⁻¹⁰¹ The parent study includes detailed menopausal status questions. In addition to these interesting phenomena, we will determine differences in cognitive outcomes based on sex. Our prior work demonstrates that although women had worse outcomes after ICH than men, but after accounting for older age, there was no significant difference⁷⁷. We will continue to explore these phenomena in the current proposal.

D 2.1 Study Timeline:

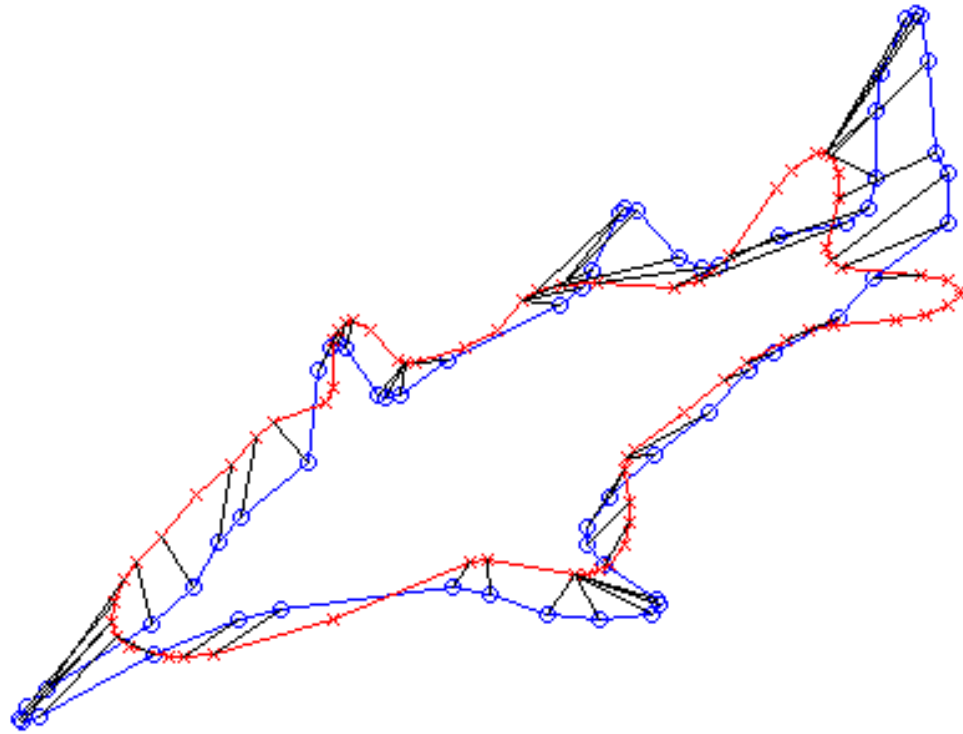
Summary and Final Thoughts

- Creativity can be practiced! Conceptual modeling is a very creative/imaginative process that you have to frequently do and practice
- After a long period of struggle, it is often when you do something completely different that inspiration arises
- The overall successful new grant ideas are typically the next step, same technique/different group, or the paradigm shift/new concept
- The overall successful investigator is great at either the big picture or the detail oriented side but can be even more successful if they practice the other side and have both sides working together

The Ant Colony Heuristic



Ultimately identifying new pathways



Be the 10% ant!

- Successful pathway versus trailblazing; do both!

Ask me anything!

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