How to Write a Successful R01

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Outline

- the process
  - peer review
  - new review criteria and scoring
- style and substance
- what not to do
- what can go wrong
- networking
- resubmissions

No Magic

- senior PI's get grants rejected/unscored
- often requires multiple submissions
  - new limit of 2 submissions (old 3)
- you need
  - good ideas
  - clear writing
  - clear signs of productivity
    - publications in good journals

The Process

- start writing early
- look for
  - RFA's (requests for applications) or
  - PA's (program announcements)
    - these are things the NIH is particularly interested in
  - http://grants.nih.gov/grants/guide/search_results.htm?year=active&scope=rfa
- Both the above programs can help get your grant funded

Timeline

- submit grants on 3x per year cycle
- typically 9 months between 1st and 2nd submission
- grants submitted June 5, not reviewed until Oct.
  - assigned to study section during this time
  - possible to submit additional data before review
  - next resubmission deadline would then be March 5.
- regular deadlines
  - June 5, Oct. 5, Feb. 5
  - resubmissions are a month later (July/Nov/March)
- some RFA's may have different deadlines

Peer Review

- Grants are assigned to specific Study Sections for review
- Cover letter can help guide grant to **correct panel**
  - Office of Extramural Research: Scientific Review Group (SRG) Roster Index
    - http://era.nih.gov/roster/index.cfm
  - call or email the Scientific Review Administrator
    - give them a 2 line summary of your project and make sure it's suitable
    - sometimes they may have suggestions on angles they are particularly interested in…
      - BUT – **caution** – their interests and the reviewers don't always coincide
  - look carefully at the makeup of the study section roster
    - get to know the members
  - don't assume you can look at the roster and determine who reviewed your grant

Cover Letter

- in the cover letter you can also request someone on the panel not to score your grant due to conflict
  - such conflicts can be personal
  - or scientific
  - a reviewer being mean or fear-inducing or suffering from some undiagnosed personality disorder - is insufficient
  - do this very sparingly
- the Program Official will want to know what the conflict is
- if the Program Official agrees that reviewer will be asked to leave the room when your grant comes up for discussion
  - it's a fairly big deal
  - so don't abuse this

Peer Review Panels

- Important to go to the **correct panel**
  - the wrong panel may not have appropriate expertise
    - end up misinterpreting things you thought were obvious
    - typically not interested in your topic if it's not their area of expertise
  - look at the composition of the panel
    - people in your field and do work you are familiar with should be on the panel
    - maybe only a handful of such people
    - networking – it's good to know people on the panel

Peer Review

- you submit your grant, it goes to the correct panel, and many months later the panel meets

- the reviewers sit around a table like this for 1-2 days
- all of these people will score your grant – only a few will actually look at it closely

Unscored.

- the first thing the panel does is get rid of at least 50% of the grants
- your **name**, grant **title**, and grant **number** are read
- 1st and 2nd reviewers are asked if they want to unscore the grant – need consensus – otherwise it will be discussed and scored
  - peer pressure to unscore grants
    - reduces work load and time people have to sit at the table
  - if unscored you get the reviewers comments
    - but no summary of the discussion (there was none)
  - they move on to the next grant...

The Reviewers.

- hopefully the reviewers are experts in your field
- each reviewer gets assigned 5-8 grants where they need to **write reviews** (1st, 2nd, or 3rd reviewer)
- each reviewer may also get another 2-5 grants that they are **readers** on
- this is a heavy load – each grant can take several hours
  - will discuss how to make your grant a pleasure to review

The Review

- 1st reviewer spends time summarizing goals, strengths and weaknesses,
  - evaluates grant following **review criteria** *
- 2nd reviewer may or may not add much
- same with the rest of the reviewers/readers

Review Criteria

- Understand the review criteria (Guidelines for Reviewers):
  - http://grants.nih.gov/grants/peer/reviewer_guidelines.htm
- **Significance**: Does the study address an important problem?
- **Approach**: Is the design/method appropriate?
- **Innovation**: Is the project original?
- **Investigators**: Are they suitable to carry out the work.
- **Environment**: Does the environment (facilities) contribute to the likelihood of success?

Scoring

- **Scoring:**
  - http://grants.nih.gov/grants/peer/reviewer_guidelines.htm
- **each of the 5 criteria below are assigned a score 1-9**
  - **1 good**
  - **9 bad**
- **Significance**: Does the study address an important problem?
- **Approach**: Is the design/method appropriate?
- **Innovation**: Is the project original?
- **Investigators**: Are they suitable to carry out the work.
- **Environment**: Does the environment contribute to the likelihood of success?
- **Ultimately you get 1 final overall score**
  - the reviewers come to a recommended consensus during their discussion or agree to a range
  - everyone at the table (even people that haven't even looked at your grant) score the grant based on the discussion they heard.
  - your final score is the mean x 10. (range 10-90)

Writing the Grant

- General Statements
- Specifics

General Guidelines

- for your first grant – don't aim too high
- R01 guidelines allow 5 years at $250k/year (modular)
- with pre-clearance you can go above this annual limit
- for first grant don't demand too much
  - ask for 3 or 4 years
  - at something less than $250k/year
  - your goal is to get into the system – prove you can manage a grant
- as a new investigator you are unproven
  - a 3 year grant at $200k/year represents much less risk in the reviewers mind
  - less likely to fund 5 years at $750k/year for a new investigator (I've seen new investigators try)

General Guidelines

- take advantage of being at Yale
- there are all sorts of experts/senior people here
- if there is some question as to expertise in an area
  - add a senior person (5% effort)

Be Careful with Novel Approaches

- Most NIH grants are a combination of some **development** and some **application** of the development to new science
  - difficult to get purely technical development grants
  - have 1 or 2 aims for development and 1 or 2 on a specific application of the method to a science problem
    - clinical translational research even better
- If Aim 1 is implementing a new method and all the subsequent aims depend on the success of this Aim you may well not get funded.
- Better to say you have an existing method that works, in Aim 1 you will improve it, and subsequent aims will either use the old method or the new one if Aim 1 is successful.

Review Criteria

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Review Criteria/Writing Style

- **make the reviewers job easy**.
- put in specific statements as to the Innovation, Significance etc...
  - more on this in a minute

Help the Reviewer

- Significance, Approach, Innovation, Investigators, Environment
- **Put summary statements at the end of each section**
- **Highlight** sections that state the **Significance**, and **Innovation**
  - "This project is significant because..."
  - "The innovation of this work is in..."
  - "This work is important because..."
- Statements that Justify your Approach (be honest with yourself and the reviewers)
  - don't use an approach that's inadequate but easy
- Emphasize in the **Preliminary Data** section how this data demonstrates you have the Expertise and Environment
  - Add Senior Faculty to your grants for needed expertise (overlap?)
  - and definitely add outside experts as consultants if you need to bolster expertise in some area

make the reviewers job easy.

Main Body Sections

- Old format: 25 pages
- Sections
  - **Specific Aims**, **Background**, **Preliminary data**, **Research Plan**.
- New format: 12 pages (Grant body), plus 1 for Specific Aims
  - essentially the same sections
  - the guidelines suggest less background and less need for detailed research plan, **only the former is true**.
  - **reviewers demand sufficient detail** to be able to judge if the experiments will work
  - **always be very <u>detailed</u>** – at 12 pages you need to learn to write concisely.

Reviewers are Lazy
(or just very busy)

- a favorite critique of the lazy reviewer is
  - "**insufficient detail** to enable me to judge the science..."
    - unscored
- provide summary statements to make their job easy
  - a reviewer may only read the Specific Aims page, and the Research Plan (skimming the latter)
  - provide **highlighted summary statements** that they can cut and paste into their reviews
    - **this will make them very happy**
  - if it is very difficult for them to summarize your proposal in a few lines **they will be unhappy**.

Specific Aims

- Spend weeks (months) on this 1 page
- **this is your grant – this sells the idea**
- on this 1 page you need to go from the very big picture (cancer is a problem, this will ultimately cure cancer)
- to the very detailed level…
- limit your Aims to 3-4 aims (3 if you do a 3 year grant)
- include Hypotheses – for the most part R01's represent Hypothesis driven research.
  - Explicitly state "We hypothesize that…" in each Aim.

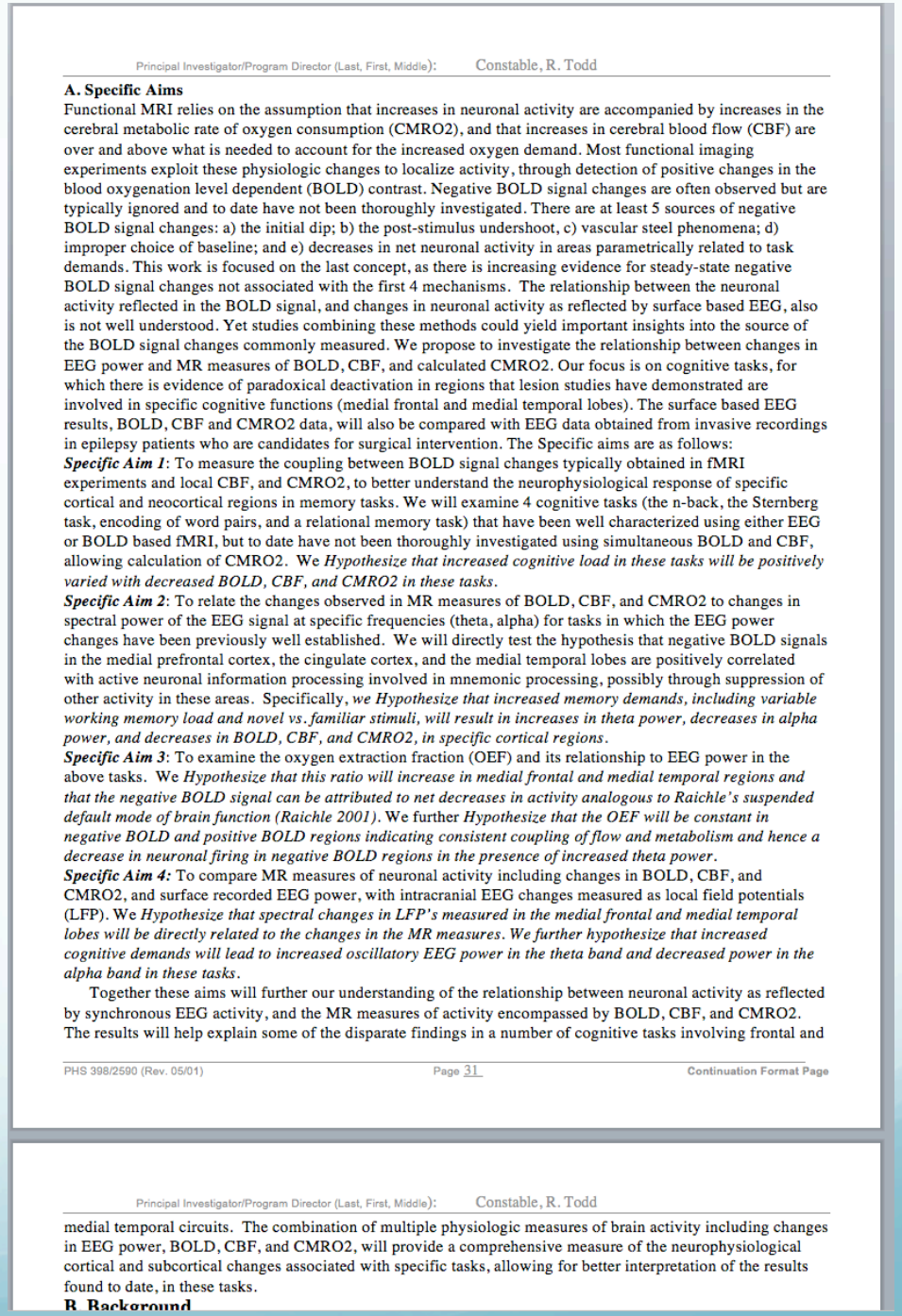
Specific Aims

This page is the CORE of your proposal.

Think about this and go over it with colleagues again and again

- **Strong short introductory paragraph**
- **Well defined Aims/reasonable Hypotheses**
- **Short Summary statement – what's unique/important – why this should be funded**

The reviewer will move from here to either look for fatal flaws if she doesn't like this page, or look for confirming evidence that this is good.



Principal Investigator/Program Director (Last, First, Middle): Constable, R. Todd

A. Specific Aims

Functional MRI relies on the assumption that increases in neuronal activity are accompanied by increases in the cerebral metabolic rate of oxygen consumption (CMRO2), and that increases in cerebral blood flow (CBF) are over and above what is needed to account for the increased oxygen demand. Most functional imaging experiments exploit these physiologic changes to localize activity, through detection of positive changes in the blood oxygenation level dependent (BOLD) contrast. Negative BOLD signal changes are often observed but are typically ignored and to date have not been thoroughly investigated. There are at least 5 sources of negative BOLD signal changes: a) the initial dip; b) the post-stimulus undershoot, c) vascular steel phenomena; d) improper choice of baseline; and e) decreases in net neuronal activity in areas parametrically related to task demands. This work is focused on the last concept, as there is increasing evidence for steady-state negative BOLD signal changes not associated with the first 4 mechanisms. The relationship between the neuronal activity reflected in the BOLD signal, and changes in neuronal activity as reflected by surface based EEG, also is not well understood. Yet studies combining these methods could yield important insights into the source of the BOLD signal changes commonly measured. We propose to investigate the relationship between changes in EEG power and MR measures of BOLD, CBF, and calculated CMRO2. Our focus is on cognitive tasks, for which there is evidence of paradoxical deactivation in regions that lesion studies have demonstrated are involved in specific cognitive functions (medial frontal and medial temporal lobes). The surface based EEG results, BOLD, CBF and CMRO2 data, will also be compared with EEG data obtained from invasive recordings in epilepsy patients who are candidates for surgical intervention. The Specific aims are as follows:

Specific Aim 1: To measure the coupling between BOLD signal changes typically obtained in fMRI experiments and local CBF, and CMRO2, to better understand the neurophysiological response of specific cortical and neocortical regions in memory tasks. We will examine 4 cognitive tasks (the n-back, the Sternberg task, encoding of word pairs, and a relational memory task) that have been well characterized using either EEG or BOLD based fMRI, but to date have not been thoroughly investigated using simultaneous BOLD and CBF, allowing calculation of CMRO2. We *Hypothesize that increased cognitive load in these tasks will be positively varied with decreased BOLD, CBF, and CMRO2 in these tasks.*

Specific Aim 2: To relate the changes observed in MR measures of BOLD, CBF, and CMRO2 to changes in spectral power of the EEG signal at specific frequencies (theta, alpha) for tasks in which the EEG power changes have been previously well established. We will directly test the hypothesis that negative BOLD signals in the medial prefrontal cortex, the cingulate cortex, and the medial temporal lobes are positively correlated with active neuronal information processing involved in mnemonic processing, possibly through suppression of other activity in these areas. Specifically, *we Hypothesize that increased memory demands, including variable working memory load and novel vs. familiar stimuli, will result in increases in theta power, decreases in alpha power, and decreases in BOLD, CBF, and CMRO2, in specific cortical regions.*

Specific Aim 3: To examine the oxygen extraction fraction (OEF) and its relationship to EEG power in the above tasks. We *Hypothesize that this ratio will increase in medial frontal and medial temporal regions and that the negative BOLD signal can be attributed to net decreases in activity analogous to Raichle's suspended default mode of brain function (Raichle 2001).* We further *Hypothesize that the OEF will be constant in negative BOLD and positive BOLD regions indicating consistent coupling of flow and metabolism and hence a decrease in neuronal firing in negative BOLD regions in the presence of increased theta power.*

Specific Aim 4: To compare MR measures of neuronal activity including changes in BOLD, CBF, and CMRO2, and surface recorded EEG power, with intracranial EEG changes measured as local field potentials (LFP). We *Hypothesize that spectral changes in LFP's measured in the medial frontal and medial temporal lobes will be directly related to the changes in the MR measures. We further hypothesize that increased cognitive demands will lead to increased oscillatory EEG power in the theta band and decreased power in the alpha band in these tasks.*

Together these aims will further our understanding of the relationship between neuronal activity as reflected by synchronous EEG activity, and the MR measures of activity encompassed by BOLD, CBF, and CMRO2. The results will help explain some of the disparate findings in a number of cognitive tasks involving frontal and

medial temporal circuits. The combination of multiple physiologic measures of brain activity including changes in EEG power, BOLD, CBF, and CMRO2, will provide a comprehensive measure of the neurophysiological cortical and subcortical changes associated with specific tasks, allowing for better interpretation of the results found to date, in these tasks.

B. Background

Background

- focus on putting the problem you are addressing in context.
- be very clear, and very generous, as to what others have done before you.
  - be sure to cite the work of people on your review panel if appropriate
- do not give the impression that you are the only one working in this field (even if you are).
- do not gloss over related work by others
  - address competing approaches head-on
  - why yours is different/better
- until this year it was best to be very generous with literature citations – now (2010) the # of cited papers is limited
- **Summarize** this section with a few sentences at the end...

Preliminary Data

- very very important to demonstrate that you have all the tools/expertise to do the work
- very important to demonstrate feasibility of your approach
- if you do not have directly relevant preliminary data work in data that is indirectly relevant but shows you have the capability etc...
- **Summary**
  - Provide a sentence or two at the end of this Section summarizing what you've shown in the prelim results

Research Plan

- reiterate the Specific Aims here and provide a Summary Paragraph (a couple of sentences) at the beginning as to the overarching goals.
  - don't make the reviewer flip back and forth from the Specific Aims page

Research Plan Format

- **D.1: Specific Aim 1** (restate the Aim and Hypotheses here)
  - **D.1.1: Design and Rationale**
  - **D.1.2: Experiment #1**, Experiment #2
  - or
  - **D.1.2: Method** (very detailed recipe here)
  - **D.1.3: Data Analysis** (very detailed step by step)
  - **D.1.4: Power Analysis** (sometimes at the end for all aims)
  - **D.1.5: Caveats/Possible Confounds** (be up front about problems – head off concerns reviewers might have)
- repeat this format for each Aim

Do Provide

- validation
  - be very clear on how you will know your result is valid.
  - provide an entire Aim on validation if possible and if reasonable
- be very specific on how you will know your result is significant
  - “We will consider a difference of $p<0.05$ to represent a significant effect.”
- be clear on the criteria for considering the experiment a success

Do Provide

- don't take 6 sentences to say 1 thing
  - say it in 1 sentence
  - use cartoons to demonstrate experiments or phenomena
  - use figures
- word heavy issues...writing is often necessarily dense because of space constraints
  - figures and cartoons with the appropriate captions can often summarize a lot of writing
- assume reader is smart but knows nothing about what you do

Do Not

- Do not go on fishing expeditions
  - “We will search for the best approach…” (pick an approach ahead of time)
  - “We will investigate this…” (sounds too exploratory)
  - “We will optimize this…” (you should already have searched and investigated and it should already be optimized)
- instead write
  - “Evidence suggests A is the best approach and we will use that, but just to be sure we will also compare with method B” (in the caveats section of each Aim)
  - “We will test the Hypothesis that…”

Do Not

- Do not have typos or formatting issues
- pay very close attention to this
- if you don't care enough – the reviewer certainly won't.
- avoid acronyms
  - some reviewers may not be in your field and will be annoyed

Alternatives

- have fallback plans
- what if Aim 1 doesn't work
- what if your hypothesis is wrong
- discuss alternative interpretations
  - requires balance here – do not want to prevaricate
  - you want to appear confident in your approach
    - but knowledgeable of other possible outcomes
    - yes – you already thought of that...

Networking

- be nice
- be generous
- it helps (if you're nice and generous) if reviewers can put a face to a name
- get to know the people in your field
  - you will review their grants and they will review yours
- at meetings – **attend poster sessions** if nothing else
  - go up to poster presenters and ask them to walk you through the poster
  - you need to talk to people and get to know them
  - hang out with your mentors and have them introduce you to people

Networking

- invite scientists in your field to come to Yale to give seminars
  - particularly people at your level
    - it's good for their cv/promotion
    - you might get invited back to their U
      - good for your cv/promotion
  - these will be your colleagues over many years
  - get to know them

After the Study Section Meeting

- scores may be posted on the commons website within days of the review meeting
- try not to check every minute for your score – every hour is probably sufficient
  - you get a score and a percentile (percentiles are sometimes posted later)
  - these days 5th-10th percentile may get funded
    - new investigators get a boost in their percentile
  - in the past it's been as high as 25th.
- **Summary Statements** take weeks (6-8) before they are posted on the Commons website

Resubmissions

- you didn't get funded 1st time around
  - hopefully you got a score
- read the reviews very carefully
- put them away for a few weeks (to cool down)
  - read them again very carefully
- call the SRO (scientific review officer) and ask for additional feedback
  - preferably in the week following the review
  - most of the are very nice and happy to provide additional comments or a sense of whether the grant is a lost cause or not

Summary Statement

- If you got a score, then in addition to the Reviewers comments, there is a paragraph that attempts to summarize the main points of the discussion of your application.
- this is followed by Reviewer 1 comments, Reviewer 2, etc...
- in the **Introduction** section of resubmission you now get only 1 page to respond to the reviewer comments

Response to Reviewers 1

- **the response is really really <u>important</u>**
- equal to the Specific Aims page in importance
- generally 2nd time around you will get some of the same reviewers and 1 or 2 new reviewers
  - the order of the reviewers will change
- the <u>first</u> thing the reviewers will do is read the previous **Summary Statement** and your response.
  - your grant will be rejected if your response is inadequate

Response to Reviewers 2

- be very polite in your response
- it is ok to disagree with a reviewers comment but do it very carefully and back it up with citations
  - not a good idea to disagree with everything
- do not skip over, or gloss over anything
  - reviewers will be looking to see that you addressed ALL previous concerns
- if you cannot address something – acknowledge that fact
  - perhaps the issue can be added as a sub-Aim to directly investigate

Response to Reviewers 3

- be very polite in your response
- if a reviewer misinterpreted something you wrote
  - don't suggest they need to read more carefully
  - apologize for being unclear and rewrite it so it is very clear
- directly address as much as you can in the response but refer to changes in specific grant Sections (e.g. see sections C.1.2 and D.2.3)
- at a minimum you need to **at least appear** to be very responsive to the reviewers comments
- quote the reviewer (r1,q2) and respond.

Response to Reviewers 4

Principal Investigator/Program Director (Last, first, middle): Constable, Robert, Todd

Response to Reviewers: We'd like to thank the reviewers for their constructive and insightful comments and are delighted they recognized that this work is potentially highly significant. Research activity in this area is rapidly increasing in the past year with much of the HBM 2009 annual meeting dedicated to this topic. We have carefully reviewed all of the comments from the reviewers and are able to respond to all the issues raised.
R1: There is little background about network theory, little about modularity: review the current state of assessing modularity, compare with the published literature: We've substantially increased the background section on network theory and modularity, include a direct comparison with Newman's modularity Aims 2 & 3.
R1: Generation of a resting atlas. While this is interesting and it would be ideal if it worked, it is likely that network structure changes from task to task. This is now discussed more extensively in section B. Actually there is substantial evidence that the intrinsic subunits do not change from task to task but that the amplitude of a given node may go up and down. The original paper by Biswal (1995) demonstrated the same motor network from resting-state data as from task data. Similarly, the default mode network can be identified through connectivity analysis during task, resting-state, or under heavy anesthesia (Vincent 2007) suggesting the intrinsic nature of the networks revealed by resting-state connectivity analysis. We present data in section B showing consistent parcellation for data obtained at rest and during a task. The strength of connections between subunits may change with task but there is no evidence that the subunits themselves change.
R1: Thus, the subunit structure also likely changes. If that is the case then a resting atlas would only be useful for rest. Eguiluz et al (PRL 94, 2005) published findings showing that the network connectivity does in fact change as the task changes. The investigators need to provide convincing evidence that a resting atlas will be useful across conditions. The reviewer is correct in pointing out that Eguiluz demonstrates changes in network properties as a function of task. There is no doubt that connectivity between different nodes changes according to task or state and we have published papers (Hampson 2006ab) as have others (Greicius 2004, Bartels 2005, Vincent 2006) demonstrating changes in connectivity between nodes as a function of task. This is very different from stating that the fundamental subunits that make up the nodes change (in defining a functional subunit we are considering the connectivity within a subunit not between subunits). As described above and in our preliminary results there is no evidence for a change at the level of the subunits. Eguiluz concludes the paper by stating that "the functional correlations… form a scale-free network with small-world properties…that are robust across parameters, subjects, and task conditions suggesting they are invariant properties of an underlying dynamical network". We agree fully with the statements in that work.
R1: Aim 1 is severely limited in that no preliminary data are presented to demonstrate feasibility of performing the analysis on the whole brain. We provide a whole brain example now in Section C with 200 parcellations.
R1: Furthermore, the study design says nothing about assessing the computational time or about validating the method with simulated and known networks. The computational time is of the order of a couple of minutes.

Get in the Game

- **start now**.
- you need good ideas and some preliminary data
- you are guaranteed not to get funded if you don't apply
- start writing grants
  - get some feedback (Summary Statements)
- there is a small window as Junior Faculty to establish that you can get funding
  - a lot of time can pass with resubmissions
  - don't wait too long

Wait-don't submit that!

- don't submit an obviously weak grant
- don't submit a grant if you wrote it in a week
- do not get a reputation for submitting garbage.
  - then when you submit something good it will not be taken seriously.
- only submit grants you have seriously and rigorously worked on

Ideas – Hopefully you have lots of them (and they're all good)

- it's best if you can have 2 (or more) good ideas on 2 separate topics that can go to 2 different study sections
  - then you can alter submissions
    - June 5, 1st submission **grant A**
    - Oct 5, 1st submission grant B
    - March 5, 2nd submission **grant A**
    - July 5, 2nd submission grant B
    - June – **grant A** funded
    - October – grant B funded
    - you're golden!
- go to private foundations for funding too – particularly ones that provide feedback (reviews)
- you should always be thinking of new grant topics and new things to get into

Reviews

- don't get discouraged
- it's tough for everyone
- don't take the reviews personally
- learn as much as you can from the reviews
- grant writing can actually be fun
  - by the end of writing a grant you rule on that topic
  - you've read the literature
  - you've organized your thoughts
  - these are good things.

Good Luck

- Questions?