Recipe for a Successful AIMS Page

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Outline

- Importance of specific aims page
- Requirements
- Standard Format
- Some Examples …

Specific Aims is the most important component of your proposal

- An overview of the whole proposal
- Reviewers 'judge' the whole proposal on this 1 page …
  - then look in proposal to confirm specifics
- Often used as a research prospectus and working guideline for working on the whole proposal
  - for getting feedback and iterating
  - Iterate (1 year or longer)

Requirements (NIH instructions)

- 1 page
- State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.
- List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.

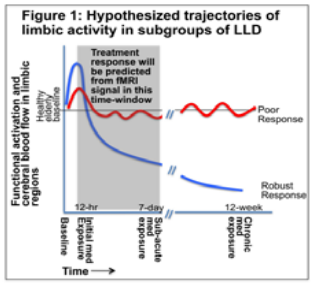
NIH SF424 form instructions

Standard Format of Specific Aims

- First few paragraphs: importance, main strategy,
- Sometimes small figure
- Specific Aims: objectives and description
  - **Visually set apart**
- Last paragraph: impact

Specific Aims: Conventional treatment of late-life depression (LLD) often requires long trials of several antidepressants before an effective regimen can be found for an individual[1]. This can take many months and is associated with persistent depressive symptoms, an increased risk of suicide, dropping out of care, and worsening of medical co-morbidities. This long response time in geriatric depression is one of the most challenging clinical features of LLD. Thus, in the elderly it is particularly important to shorten this window, and to identify as early as possible what medication regimen will be the most effective for an individual patient. Predictors of treatment response are a focus of both personalized clinical care and translational bench-to-bedside research, both of which are priority aims of the NIMH strategic plan[2]. Recently, with the development of Pharmacologic Functional MRI (phMRI[3]), it has become possible to track cerebral blood flow patterns (as proxies of regional brain activity) in response to the initiation and titration of a medication. This approach may be used to find the earliest point at which brain activity in LLD can be used to predict treatment response.

The proposed study is a continuation of R01MH076079, now in its 5th year. During the previous funding cycle this research program has studied a model of altered connectivity in LLD and identified patterns of Functional MRI (fMRI) activity associated with treatment response. The hypotheses for this continuation follow from a surprising finding from the current R01: in LLD (contrary to findings in mid-life depression[4-8]) high rostral anterior cingulate (rACC) activity pre-treatment does NOT predict a better treatment response. In fact, we found the opposite; in the elderly, we found a trend for high pre-treatment rACC activity to predict worse treatment response. This pattern can be partially explained by the overlay of age-related structural brain changes (in this case, white matter hyperintensity, WMH, burden), which are also associated with increased rACC activity. That is, in the elderly, pre-treatment fMRI appears particularly confounded as a predictor of antidepressant response.



Although pre-treatment rACC hyper-activity was not a significant predictor of treatment response in our study, we did find that a decrease in rACC fMRI activity over time was correlated with better response to antidepressant treatment. Thus, our findings suggest that, in the elderly, the *trajectory* of fMRI activity associated with initiating and maintaining an antidepressant is potentially useful at identifying the earliest point that characterizes an individual's clinical response (Figure 1). Based on previous work (Sections B & C8), we believe that this 'Tipping Point' occurs between the initial medication exposure and 7 days later. This proposal is innovative in defining this window by measuring activation at both 12-hours (initial medication exposure) and 7-days into treatment (sub-acute exposure); the novelty of this proposal lies in characterizing acute and chronic fMRI changes in response to pharmacotherapy.

The proposed study leverages the resources of a recently funded large NIH clinical treatment trial of Venlafaxine XR (VENLA) to treat geriatric depression (IRLGREY, PI: Reynolds, R01MH083648, Section D.2). Subject recruitment, characterization, and treatment are covered primarily by IRLGREY. A 1-day placebo lead-in is added to IRLGREY to help distinguish medication effects from placebo response. The brain regions and fMRI tasks follow from the literature, including our work, which highlight the relevance of a ventral circuit[9; 10], often referred to as limbic, including amygdala, rACC, and anterior insula. These regions are associated with overlapping affective processing functions, including affective reactivity, affective regulation, and affective awareness (or perception). The patterns of fMRI activation will be characterized using mixture trajectory modeling[11], particularly appropriate for the proposed sparse temporal sampling. The aims are:

Aim 1: To characterize the trajectories of the phMRI responses to serotonin reuptake inhibition in LLD.
H.1 phMRI limbic activation (rACC, insula, and amygdala) over the course of treatment with VENLA will follow at least 2 distinct trajectories, with different levels of final (12-week) limbic activation.
H.2 The primary two trajectories (found in H.1) will diverge by 7 days (and perhaps as early as 12 hours).
Aim 2: To identify the phMRI predictors of the treatment response in LLD. We hypothesize that the trajectories of limbic activity characterized in Aim 1 will predict clinical response to treatment.
H.1 The phMRI trajectory from baseline to 7 days (and perhaps as early as 12 hours) will predict the 12-week response to treatment, as measured by percent drop in Montgomery-Asberg score.
H.2. Predictors in H.1 will remain significant after controlling for age, gender, structural MRI, cognition, and clinical features, supporting the functional neuroanatomy as an endophenotype of LLD.
Exploratory Aim: To relate markers of age-related white matter disease (structural MRI brain abnormalities and cognitive function) to phMRI treatment-response trajectories in LLD.
H.1 WMH burden, altered structural and functional connectivity (DTI and fMRI), and decreased cognition (especially information processing speed) will all be associated with increased baseline limbic reactivity.
H.2 The effect of age-related markers of neuropathology (MRI and cognitive measures listed in H.1 above) on treatment response will be mediated by the 7-day (and possibly 12-hour) phMRI trajectory.
IMPACT: The proposed study is designed to impact both ends of the translational research path: from characterizing the pharmacologic effects in the brain to the potential clinical use of MRI for personalized treatment. As far as we are aware, this will be the first study to systematically characterize the trajectory of fMRI limbic activity to an SRI, for any age group. The study focuses on the elderly because the importance of predicting treatment response in that group has added urgency due to their prolonged response to treatment and high suicide risk.

Standard Format of Specific Aims

- First few paragraphs: importance, main strategy,
- Sometimes small figure
- Specific Aims: objectives and description
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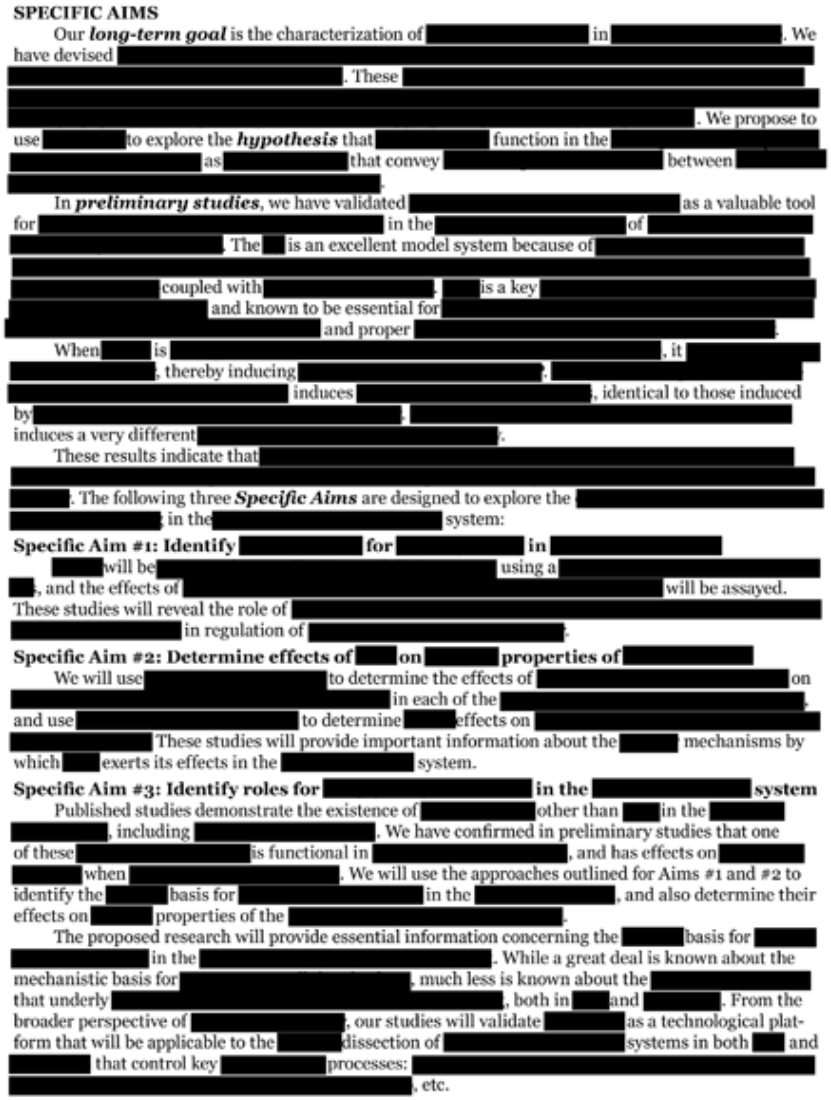

SPECIFIC AIMS

Our ***long-term goal*** is the characterization of [redacted] in [redacted]. We have devised [redacted]. These [redacted]. We propose to use [redacted] to explore the ***hypothesis*** that [redacted] function in the [redacted] as [redacted] that convey [redacted] between [redacted].

In ***preliminary studies***, we have validated [redacted] as a valuable tool for [redacted] in the [redacted] of [redacted]. The [redacted] is an excellent model system because of [redacted] coupled with [redacted], [redacted] is a key [redacted] and known to be essential for [redacted] and proper [redacted].

When [redacted] is [redacted], it [redacted], thereby inducing [redacted], [redacted] induces [redacted], identical to those induced by [redacted], [redacted] induces a very different [redacted].

These results indicate that [redacted]. The following three ***Specific Aims*** are designed to explore the [redacted], in the [redacted] system:

Specific Aim #1: Identify [redacted] for [redacted] in [redacted]

[redacted] will be [redacted] using a [redacted], and the effects of [redacted] will be assayed. These studies will reveal the role of [redacted] in regulation of [redacted].

Specific Aim #2: Determine effects of [redacted] on [redacted] properties of [redacted]

We will use [redacted] to determine the effects of [redacted] on [redacted] in each of the [redacted], and use [redacted] to determine [redacted] effects on [redacted]. These studies will provide important information about the [redacted] mechanisms by which [redacted] exerts its effects in the [redacted] system.

Specific Aim #3: Identify roles for [redacted] in the [redacted] system

Published studies demonstrate the existence of [redacted] other than [redacted] in the [redacted], including [redacted]. We have confirmed in preliminary studies that one of these [redacted] is functional in [redacted], and has effects on [redacted] when [redacted]. We will use the approaches outlined for Aims #1 and #2 to identify the [redacted] basis for [redacted] in the [redacted], and also determine their effects on [redacted] properties of the [redacted].

The proposed research will provide essential information concerning the [redacted] basis for [redacted] in the [redacted]. While a great deal is known about the mechanistic basis for [redacted], much less is known about the [redacted] that underly [redacted], both in [redacted] and [redacted]. From the broader perspective of [redacted], our studies will validate [redacted] as a technological platform that will be applicable to the [redacted] dissection of [redacted] systems in both [redacted] and [redacted] that control key [redacted] processes: [redacted], etc.

(DrugMonkey website)

Specific Aims

- Usually 2-4 aims
  - More is hard to support in a 12-page application
  - Additional use of data can be described as added value of dataset, but can't put them all as aims

- 2-4 testable hypotheses for each aim

- Exploratory aims can be used
  - power not necessary

Other points

- Aims & hypotheses should be succinct very clear
- Hypotheses should be clearly testable
  - Reviewer can anticipate the analysis plan
- Aims should be related to each other
  - But, be careful that they are not too dependent – if Hypotheses are contradicted in 1st aim, do other aims still have value?

Address review criteria

- **Impact**
- Significance
- Investigator
- Innovation
- Approach
- Environment

- In proposal it can be helpful to explicitly highlight the strengths in each area. Makes reviewers job easier.
- In specific aims page focusing on strength of significance, innovation, and approach. Can be helpful to highlight how this follows from investigators work, and strength of environment.

Identify study section

- Important to know audience that will be reviewing.
- Talk with program officer
- Align with program priorities (but still writing for peer review)

Example

First few paragraphs, describe importance and overview of proposal

<u>Specific Aims:</u> [[start with why important]] Conventional treatment of late-life depression (LLD) often requires long trials of several antidepressants before an effective regimen can be found for an individual[1]. …with the development of Pharmacologic Functional MRI (phMRI[3]), it has become possible to track cerebral blood flow patterns (as proxies of regional brain activity) in response to the initiation and titration of a medication. This approach may be used to find the earliest point at which brain activity in LLD can be used to predict treatment response. ….

[[overview and strengths of approach]] The proposed study leverages the resources of a recently funded large NIH clinical treatment trial of Venlafaxine XR (VENLA) to treat geriatric depression (IRLGREY, PI: Reynolds, R01MH083648, Section D.2). Subject recruitment, characterization, and treatment are covered primarily by IRLGREY….The patterns of fMRI activation will be characterized using mixture trajectory modeling[11], particularly appropriate for the proposed sparse temporal sampling. The aims are:

Aims

Aim 1: To characterize the trajectories of the phMRI responses to serotonin reuptake inhibition in LLD. H.1 phMRI limbic activation (rACC, insula, and amygdala) over the course of treatment with VENLA will follow at least 2 distinct trajectories, with different levels of final (12-week) limbic activation.

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Exploratory Aim: To relate markers of age-related white matter disease (structural MRI brain abnormalities and cognitive function) to phMRI treatment-response trajectories in LLD.

H.1 WMH burden, altered structural and functional connectivity (DTI and fMRI), and decreased cognition (especially information processing speed) will all be associated with increased baseline limbic reactivity.

H.2 The effect of age-related markers of neuropathology (MRI and cognitive measures listed in H.1 above) on treatment response will be mediated by the 7-day (and possibly 12-hour) phMRI trajectory.

Final Impact Statement

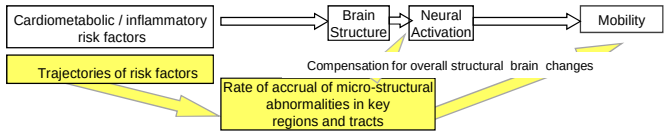
IMPACT: The proposed study is designed to impact both ends of the translational research path: from characterizing the pharmacologic effects in the brain to the potential clinical use of MRI for personalized treatment. As far as we are aware, this will be the first study to systematically characterize the trajectory of fMRI limbic activity to an SRI, for any age group. The study focuses on the elderly because the importance of predicting treatment response in that group has added urgency due to their prolonged response to treatment and high suicide risk.

Another Example (MPI: Rosano, Aizenstein)

Specific Aims.
Slowing gait and difficulty walking are major and common problems of older adults, they worsen with age and they are associated with greater risk of disability, hospitalization and death.[2-4] Slower gait is associated with macro-structural brain abnormalities, specifically with white matter hyperintensities (WMH) distributed throughout the overall brain. While older adults with greater overall WMH walk more slowly and are **vulnerable** to greater mobility decline, the converse relationship also holds. Elderly with relatively little overall WMH tend to have preserved mobility, and thus appear to be **protected**. Our preliminary data suggest there is another group of elderly, who have preserved mobility and function despite substantial overall WMH. The prevalence of this **resilience',** or **maintenance of function in the face of overall WMH**, is consistently high in our two preliminary studies About 20% of our participants have substantial WMH and faster than expected mean gait, and, compared to those with high WMH and slower gait, they have greater 15-year survival rate and normal information-processing speed, a cognitive domain strongly related to mobility.

We propose that this apparent **resilience** is related to slower accrual of micro-structural abnormalities and unique neural activation patterns within critical mobility-related regions and tracts **(Figure 1)**. Specifically, we hypothesize that slower accrual of focal micro-structural abnormalities within fronto-parietal networks offsets the impact of overall WMH on function, possibly through higher neural activation. Slower longitudinal worsening of risk factors (blood pressure, interleukin-6 and glucose) may contribute to slowing down the accrual of micro-structural abnormalities and thus maintain function.

Figure 1: Model to explain resilience = maintenance of function in the face of structural brain abnormalities



White text boxes and arrows= High levels of risk factors (e.g. blood pressure, IL-6, glucose) can contribute to structural brain abnormalities (high overall WMH), which impairs neural activation and ultimately function. This model does not account for resilience = brain abnormalities and maintained mobility.
Colored text boxes and arrows =Slower longitudinal trajectories of accumulation of risk factors (e.g., BP rising slowly over time) would in turn slow down the longitudinal accrual of micro-structural abnormalities in fronto-parietal networks and thus facilitate compensatory neural activation and maintained function.

Accrual of micro-structural abnormalities and neural activation are not visible on standard structural MRI obtained at one time point and require advanced longitudinal MRI methodology. In this dual PI project, Drs. Rosano and Aizenstein propose to acquire a repeat brain MRI in participants of a longitudinal NIA epidemiologic study - the Health ABC (Health, Aging and Body Composition) Study - ongoing since 1996. A total of 325 Health ABC participants had received a 1st brain MRI in 2007-08 with measures of micro-structure (PI: Dr. Rosano, K23AG028966-01,R01AG029232). The 2nd (proposed) MRI will include repeat structural measures and new neural activation measures. The structural image acquisition methods of the 1st MRI and the 2nd (proposed) MRI are identical, thus yielding 3 years longitudinal accrual of structural abnormalities within fronto-parietal networks. The project will also collect new mobility measures for 3 years after the 2nd MRI and it assesses the impact of brain abnormalities on function while accounting for other key **contributors of mobility** (lower extremity peripheral nerve and muscle strength, body composition, cardiopulmonary and chronic health conditions). This proposal cost-effectively leverages existing longitudinal data on cardiometabolic and inflammatory risk factors, as well as hospitalization and strokes ascertained since 1996. The three Aims are:

Aim 1: Characterize functional and structural neuroimaging features of 'resilience' [illegible]
H.1. 'Resilient' adults have greater neural activation at 2nd MRI within fronto-parietal networks while performing information-processing tasks with similar accuracy, as compared with the 'Protected' and overall greater neural activation and accuracy as compared to the 'Vulnerable'
H.2. 'Resilient' adults have had a slower accrual of micro-structural abnormalities within fronto-parietal networks (from 1st to 2nd MRI), compared to the 'Vulnerable' adults and more similar to the 'Protected'

Aim 2: Test interrelationships between functional and structural neuroimaging features of 'resilience'
H.1. Slower accrual rate of micro-structural abnormalities within fronto-parietal networks (from 1st to 2nd MRI) is associated with greater neural activation while performing information-processing tasks (at 2nd MRI).
H.2 Accrual rate of micro-structural abnormalities within the fronto-parietal networks (from 1st to 2nd MRI) attenuates the association of WMH with neural activation (at the 2nd MRI). Specifically, higher WMH and increased neural activation will occur in the context of slower accrual of micro-structural abnormalities.

Aim 3: Explore potential explanatory factors of 'resilience'
H.1. Favorable risk factor profiles (slower longitudinal increases in blood pressure, fasting glucose, interleukin-6, measured from baseline to 1st MRI) are associated with subsequent slower accrual of micro-structural abnormalities, independently of the absolute risk factor value and of contributors of slow gait.
H.2. Favorable risk factor profiles are associated with subsequent lower mobility decline (through 3 years after the 2nd MRI) independently of the absolute risk factor value and of other contributors of slow gait.
H.3. Slower accrual rate of micro-structural abnormalities within fronto-parietal networks is associated with subsequent lower mobility decline independently of other contributors of slow gait.
H.4. Slower accrual rate of micro-structural abnormalities attenuates the associations in H.2.

- Standard format – left out final impact statement
- Figure for conceptual model

Specific Aims.

[[start with why care]] Slowing gait and difficulty walking are major and common problems of older adults, they worsen with age and they are associated with greater risk of disability, hospitalization and death.[2-4] Slower gait is associated with macro-structural brain abnormalities, specifically with white matter hyperintensities (WMH) distributed throughout the overall brain. While older adults with greater overall WMH walk more slowly and are **vulnerable** to greater mobility decline, the converse relationship also holds. Elderly with relatively little overall WMH tend to have preserved mobility, and thus appear to be **protected**. Our preliminary data suggest there is another group of elderly, who have preserved mobility and function despite substantial overall WMH. The prevalence of this '**resilience',** or **maintenance of function in the face of overall WMH**, is consistently high in our two preliminary studies About 20% of our participants have substantial WMH and faster than expected mean gait, and, compared to those with high WMH and slower gait, they have greater 15-year survival rate and "normal" information-processing speed, a cognitive domain strongly related to mobility.

- **Discussion of preliminary data helps to show strength of investigator, team, feasibility …**

Aim 1: Characterize functional and structural neuroimaging features of 'resilience': [illegible] **'Resilient'** [illegible] **'Protected'** [illegible] **'Vulnerable'** [illegible]

H.1. '*Resilient*' adults have greater neural activation at 2nd MRI within fronto-parietal networks while performing information-processing tasks with similar accuracy, as compared with the *'Protected'* and overall greater neural activation and accuracy as compared to the *'Vulnerable'*.

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H.3. Slower accrual rate of micro-structural abnormalities within fronto-parietal networks is associated with subsequent lower mobility decline independently of other contributors of slow gait.

H.4. Slower accrual rate of micro-structural abnormalities attenuates the associations in H.2.

- First aim is often more conservative, extending preliminary data.
- 2nd and 3rd become more integrative and speculative.

Another Example… (from 2006)

Principal Investigator/Program Director (Last, First, Middle): Aizenstein, Howard, Jay

A. SPECIFIC AIMS

Depression in the elderly is common and causes significant distress and disability. Approximately 15% of the elderly have significant depressive symptoms (Beekman et al., 1999). Depression is the 2nd leading cause of 'global disease burden' (Murray & Lopez, 1996), the leading predictor of poor outcome from medical illnesses such as heart disease (Frasure-Smith et al., 1993; Schulz et al., 2000), and the primary diagnosis in most elderly suicides (Conwell et al., 1996). Moreover, demographics are shifting and the number of elderly is expected to double by 2030 (The Administration on Aging, 2003), further increasing the public health significance of late-life depression (LLD). Unfortunately, current depression treatments, which are borrowed from the treatment of mid-life depression, are only partly effective in the elderly; it is estimated that 40-50% of those with LLD have a delayed or limited response to first-line antidepressant treatment. The long-term goal of the proposed study is to improve LLD treatments through a better understanding of the neurobiology.

The primary aim of this R01 application is to characterize the functional neuroanatomy of geriatric major depression and use this to explain treatment response variability. The identified functional neuroanatomy and treatment response subgroups can then serve as targets for future LLD prevention and treatment studies. The proposed study will identify in elderly individuals the changes in regional brain activity associated with being depressed, being treated for depression, and responding to depression treatment. To this end we will investigate, with functional MRI (fMRI), three of the key cognitive and affective neural pathways associated with LLD. The three pathways that we will investigate are a) cognitive control, b) declarative memory, and c) affective reactivity. These are central to theories of LLD and, as illustrated in Figure 1, are associated with specific brain regions that have been linked to the neurobiology of LLD: the lateral prefrontal cortex (LPFC), the dorsal anterior cingulate cortex (dACC), the medial temporal lobe (MTL), and the amygdala. In the specific tasks, subjects will inhibit a prepotent response (cognitive control), recognize previously seen words (declarative memory), and respond to faces expressing emotion (affective reactivity). The brain regions and connections identified in Figure 1 are a simplification of the actual neuroanatomy, and meant to summarize the general brain regions, cognitive/affective circuits, and functional connections that are the focus of this grant. A more detailed version of Figure 1 appears later as Figure 2.

Our guiding hypothesis is that depression in elderly individuals is uniquely characterized by altered functional connectivity within the cognitive and affective neural pathways that mediate cognitive control, declarative memory, and affective reactivity. Although LLD is characterized by marked heterogeneity in phenotype (e.g., variability in cognitive impairment) and mechanism (e.g., neurodegeneration, cerebrovascular disease, and monoamine dysregulation) we suggest that a common unifying theme in the disorder is altered functional connectivity, as manifested by lack of coordinated activity of the LPFC with the ACC during executive tasks, with the hippocampus during declarative memory encoding, and with the amygdala during affective processing. There is evidence of functional disconnection in mid-life depression, as in LLD. The current proposal focuses on testing the altered connectivity model within LLD, where we believe the functional disconnection will be more prominent (than in mid-life depression), in part because of greater damage to prefrontal white matter tracts due to cerebrovascular and neurodegenerative damage.

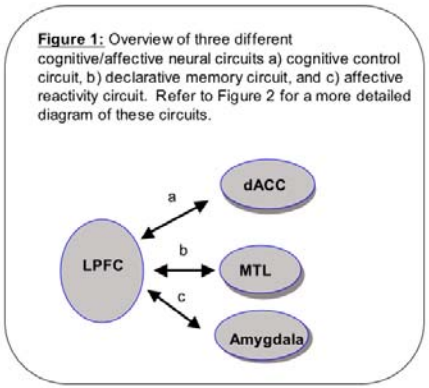

Figure 1: Overview of three different cognitive/affective neural circuits a) cognitive control circuit, b) declarative memory circuit, and c) affective reactivity circuit. Refer to Figure 2 for a more detailed diagram of these circuits.

In order to pursue this goal we will use the joint infrastructure of the Pittsburgh Intervention Research Center for Late-Life Mood Disorders (IRC/LLMD, MH-52247), which will transition in March 2005 to an Advanced Center for Interventions and Services Research for Late-Life Mood Disorders (ACISR/LLMD, MH-71944), and the Pittsburgh Alzheimer's Disease Research Center (ADRC; AG05133). We will evaluate 120 elderly subjects: 40 elderly control subjects and 80 with LLD. The LLD group will be over-sampled to power the study for analyses of the effect of cognitive impairment in LLD. To limit heterogeneity in the sample and focus on a subgroup most distinct from mid-life depression, we will restrict the depressed subjects to those with late-onset late-life depression (onset of first lifetime depressive episode at age 60 or greater). Subjects will undergo fMRI both before and after escitalopram treatment for their depression (delivered as part of two ongoing late-life depression treatment studies, MH-37869 & MH-43832). The pre-treatment data will be used to test the altered connectivity model in LLD pre-treatment (Specific Aim 1) and to predict treatment response variability (Specific Aim 3). The post-treatment data will be used to further support the altered connectivity model by showing in Specific Aim 2 that the altered connectivity with depression persists despite depression treatment.

Aim 1: Characterize the functional neuroanatomy of LLD pre-treatment.

Hypotheses:

1a. On all 3 tasks (cognitive control, declarative memory, and affective reactivity) LLD will be associated with regional disturbances in functional activation: decreased LPFC activation on all tasks, decreased ACC activation on the executive control task, decreased MTL activation on the declarative memory task, and increased amygdala activation on the affective reactivity task.

1b. Altered functional connectivity in cognitive and affective processing will be evidenced during the identified cognitive and affective tasks, by significantly lower (compared to non-depressed controls) correlations between the LPFC activation and activation in the three other regions of interest: the ACC, the MTL, and the Amygdala,

Aim 2: Characterize the functional neuroanatomy of LLD post-pharmacotherapy.

Hypotheses:

2a. The pre-treatment regional fMRI differences posited in Hypothesis 1b will resolve in response to depression treatment.

2b. The pre-treatment altered functional connectivity hypothesized in Aim 1 (and evidenced by decreased correlation) will persist after depression treatment.

Aim 3: Investigate the biological basis for treatment resistance in LLD.

Hypothesis 3. Altered fMRI measures on the three cognitive and affective circuits will predict time to treatment response. Specifically, we predict that the combined effects of the fMRI response on each of the three cognitive and affective circuits will be significantly associated with time to treatment response. Moreover, we expect that functional connectivity will be associated with treatment response above and beyond the effect of regional fMRI changes.

Additional Exploratory Aim: Characterize the relation of the BOLD fMRI response to variability in brain structure and cognition.

Exploratory Hypotheses: Our primary aims follow from our belief that structural brain changes, associated with neurodegeneration and cerebrovascular disease, lead to altered regional activity as well as altered functional connectivity, and that these changes in brain function are intimately tied to the depressive syndrome (including cognitive changes). While the focus of this research study is in testing our hypothesis of the relations of these functional measures to LLD, an additional test of our model would be to show the relationship of the fMRI measures obtained in this study to structural brain measures (i.e., white matter integrity, as measured by white matter hyperintensity, WMH, ratings or diffusion tensor imaging, DTI) and cognitive functioning. As an exploratory aim we will use the structural brain measures that are available on these subjects as part of their participation in the IRC/LLMD (WMH ratings) and correlate these measures with the fMRI data acquired as part of this study. Additionally, we will use IRC/LLMD neuropsychological data and the ADRC adjudicated diagnoses to characterize the relation of the fMRI measures to both cognitive impairment and cognitive impairment diagnoses in LLD.

This study represents a continuation of the research plan from Dr. Aizenstein's K23 career development award in which he refined methods for fMRI in aging and conducted a pilot fMRI study of LLD. The changes in regional activity and altered connectivity suggested in the pilot study will be examined in the current study with a fully-powered hypothesis-driven design.

B. BACKGROUND AND SIGNIFICANCE

List of Abbreviations

ACC: *Anterior Cingulate Cortex*	***HRF:*** *hemodynamic response function*
BA: *Brodmann Area*	***LLD****: Late-life depression, used interchangeably with geriatric depression*
BOLD: *Blood Oxygen Level Dependent signal (the physiologic proxy of neural activity that is measured with fMRI).*	***LPFC:*** *Lateral Prefrontal Cortex (specifically Brodmann Areas 9, 44, 45, 46, & 47).*
dACC: *Dorsal Anterior Cingulate Cortex*	***MTL****: Medial Temporal Lobe, including hippocampal region (CA fields, dentate gyrus, and subicular complex) and the adjacent perirhinal, entorhinal, and parahippocampal cortices.*
DTI: *Diffusion Tensor Imaging*	

Another Example… (from 2006)

Principal Investigator/Program Director (Last, First, Middle): Aizenstein, Howard, Jay

A. SPECIFIC AIMS

Depression in the elderly is common and causes significant distress and disability. Approximately 15% of the elderly have significant depressive symptoms (Beekman et al., 1999). Depression is the 2nd leading cause of 'global disease burden' (Murray & Lopez, 1996), the leading predictor of poor outcome from medical illnesses such as heart disease (Frasure-Smith et al., 1993; Schulz et al., 2000), and the primary diagnosis in most elderly suicides (Conwell et al., 1996). Moreover, demographics are shifting and the number of elderly is expected to double by 2030 (The Administration on Aging, 2003), further increasing the public health significance of late-life depression (LLD). Unfortunately, current depression treatments, which are borrowed from the treatment of mid-life depression, are only partly effective in the elderly; it is estimated that 40-50% of those with LLD have a delayed or limited response to first-line antidepressant treatment. The long-term goal of the proposed study is to improve LLD treatments through a better understanding of the neurobiology.

The primary aim of this R01 application is to characterize the functional neuroanatomy of geriatric major depression and use this to explain treatment response variability. The identified functional neuroanatomy and treatment response subgroups can then serve as targets for future LLD prevention and treatment studies. The proposed study will identify in elderly individuals the changes in regional brain activity associated with being depressed, being treated for depression, and responding to depression treatment. To this end we will investigate, with functional MRI (fMRI), three of the key cognitive and affective neural pathways associated with LLD. The three pathways that we will investigate are a) cognitive control, b) declarative memory, and c) affective reactivity. These are central to theories of LLD and, as illustrated in Figure 1, are associated with specific brain regions that have been linked to the neurobiology of LLD: the lateral prefrontal cortex (LPFC), the dorsal anterior cingulate cortex (dACC), the medial temporal lobe (MTL), and the amygdala. In the specific tasks, subjects will inhibit a prepotent response (cognitive control), recognize previously seen words (declarative memory), and respond to faces expressing emotion (affective reactivity). The brain regions and connections identified in Figure 1 are a simplification of the actual neuroanatomy, and meant to summarize the general brain regions, cognitive/affective circuits, and functional connections that are the focus of this grant. A more detailed version of Figure 1 appears later as Figure 2.

Our guiding hypothesis is that depression in elderly individuals is uniquely characterized by altered functional connectivity within the cognitive and affective neural pathways that mediate cognitive control, declarative memory, and affective reactivity. Although LLD is characterized by marked heterogeneity in phenotype (e.g., variability in cognitive impairment) and mechanism (e.g., neurodegeneration, cerebrovascular disease, and monoamine dysregulation) we suggest that a common unifying theme in the disorder is altered functional connectivity, as manifested by lack of coordinated activity of the LPFC with the ACC during executive tasks, with the hippocampus during declarative memory encoding, and with the amygdala during affective processing. There is evidence of functional disconnection in mid-life depression, as in LLD. The current proposal focuses on testing the altered connectivity model within LLD, where we believe the functional disconnection will be more prominent (than in mid-life depression), in part because of greater damage to prefrontal white matter tracts due to cerebrovascular and neurodegenerative damage.

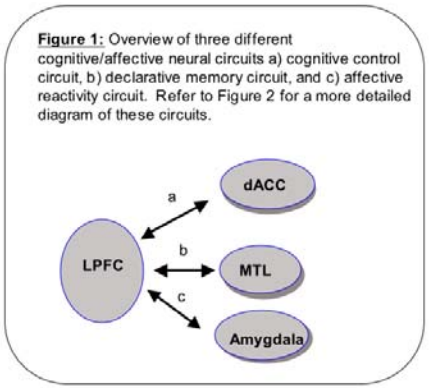

Figure 1: Overview of three different cognitive/affective neural circuits a) cognitive control circuit, b) declarative memory circuit, and c) affective reactivity circuit. Refer to Figure 2 for a more detailed diagram of these circuits.

In order to pursue this goal we will use the joint infrastructure of the Pittsburgh Intervention Research Center for Late-Life Mood Disorders (IRC/LLMD, MH-52247), which will transition in March 2005 to an Advanced Center for Interventions and Services Research for Late-Life Mood Disorders (ACISR/LLMD, MH-71944), and the Pittsburgh Alzheimer's Disease Research Center (ADRC; AG05133). We will evaluate 120 elderly subjects: 40 elderly control subjects and 80 with LLD. The LLD group will be over-sampled to power the study for analyses of the effect of cognitive impairment in LLD. To limit heterogeneity in the sample and focus on a subgroup most distinct from mid-life depression, we will restrict the depressed subjects to those with late-onset late-life depression (onset of first lifetime depressive episode at age 60 or greater). Subjects will undergo fMRI both before and after escitalopram treatment for their depression (delivered as part of two ongoing late-life depression treatment studies, MH-37869 & MH-43832). The pre-treatment data will be used to test the altered connectivity model in LLD pre-treatment (Specific Aim 1) and to predict treatment response variability (Specific Aim 3). The post-treatment data will be used to further support the altered connectivity model by showing in Specific Aim 2 that the altered connectivity with depression persists despite depression treatment.

Aim 1: Characterize the functional neuroanatomy of LLD pre-treatment.

Hypotheses:

1a. On all 3 tasks (cognitive control, declarative memory, and affective reactivity) LLD will be associated with regional disturbances in functional activation: decreased LPFC activation on all tasks, decreased ACC activation on the executive control task, decreased MTL activation on the declarative memory task, and increased amygdala activation on the affective reactivity task.

1b. Altered functional connectivity in cognitive and affective processing will be evidenced during the identified cognitive and affective tasks, by significantly lower (compared to non-depressed controls) correlations between the LPFC activation and activation in the three other regions of interest: the ACC, the MTL, and the Amygdala,

Aim 2: Characterize the functional neuroanatomy of LLD post-pharmacotherapy.

Hypotheses:

2a. The pre-treatment regional fMRI differences posited in Hypothesis 1b will resolve in response to depression treatment.

2b. The pre-treatment altered functional connectivity hypothesized in Aim 1 (and evidenced by decreased correlation) will persist after depression treatment.

Aim 3: Investigate the biological basis for treatment resistance in LLD.

Hypothesis 3. Altered fMRI measures on the three cognitive and affective circuits will predict time to treatment response. Specifically, we predict that the combined effects of the fMRI response on each of the three cognitive and affective circuits will be significantly associated with time to treatment response. Moreover, we expect that functional connectivity will be associated with treatment response above and beyond the effect of regional fMRI changes.

Additional Exploratory Aim: Characterize the relation of the BOLD fMRI response to variability in brain structure and cognition.

Exploratory Hypotheses: Our primary aims follow from our belief that structural brain changes, associated with neurodegeneration and cerebrovascular disease, lead to altered regional activity as well as altered functional connectivity, and that these changes in brain function are intimately tied to the depressive syndrome (including cognitive changes). While the focus of this research study is in testing our hypothesis of the relations of these functional measures to LLD, an additional test of our model would be to show the relationship of the fMRI measures obtained in this study to structural brain measures (i.e., white matter integrity, as measured by white matter hyperintensity, WMH, ratings or diffusion tensor imaging, DTI) and cognitive functioning. As an exploratory aim we will use the structural brain measures that are available on these subjects as part of their participation in the IRC/LLMD (WMH ratings) and correlate these measures with the fMRI data acquired as part of this study. Additionally, we will use IRC/LLMD neuropsychological data and the ADRC adjudicated diagnoses to characterize the relation of the fMRI measures to both cognitive impairment and cognitive impairment diagnoses in LLD.

This study represents a continuation of the research plan from Dr. Aizenstein's K23 career development award in which he refined methods for fMRI in aging and conducted a pilot fMRI study of LLD. The changes in regional activity and altered connectivity suggested in the pilot study will be examined in the current study with a fully-powered hypothesis-driven design.

B. BACKGROUND AND SIGNIFICANCE

List of Abbreviations

ACC: *Anterior Cingulate Cortex*	***HRF:*** *hemodynamic response function*
BA: *Brodmann Area*	***LLD****: Late-life depression, used interchangeably with geriatric depression*
BOLD: *Blood Oxygen Level Dependent signal (the physiologic proxy of neural activity that is measured with fMRI).*	***LPFC:*** *Lateral Prefrontal Cortex (specifically Brodmann Areas 9, 44, 45, 46, & 47).*
dACC: *Dorsal Anterior Cingulate Cortex*	***MTL****: Medial Temporal Lobe, including hippocampal region (CA fields, dentate gyrus, and subicular complex) and the adjacent perirhinal, entorhinal, and parahippocampal cortices.*
DTI: *Diffusion Tensor Imaging*	

Another Example… (from 2006)

- Was not always limited to 1-page
- Previous 25 page limit, allowed space to justify more aims

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Thanks

- Discussion & Questions?