The Coaching for Cognition in Alzheimer's (COCOA) Trial

COCOA
Coaching for Cognition in Alzheimer's

COCOA is supported by Providence St. Joseph Health.

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Institute for Systems Biology

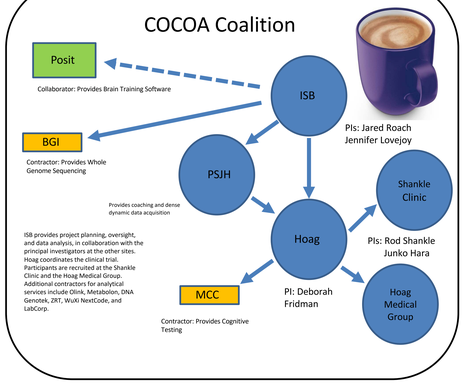
Motivation

- The COCOA Trial is part of the PSJH Alzheimer's Pillar – a collaboration between ISB and Providence St. Joseph Health to revolutionize prevention and treatment of Alzheimer's disease (AD).
- COCOA is a clinical trial designed to prevent, delay, or reverse AD.
- We will test the effectiveness of coaching for cognitive wellness and healthy aging for individuals with Mild Cognitive Impairment (MCI) or early AD, emphasizing diet, exercise, and brain training.
- We will pioneer new methods for clinical trials.
- We will uncover and understand relevant molecular, genetic, and environmental mechanisms.

Abstract

Background: Comprehensive treatment of Alzheimer's disease requires management of medical conditions and lifestyle modifications. Adherence to lifestyle approaches varies widely. We hypothesize that data-driven health coaching enhances compliance with lifestyle interventions, and that inclusion of these interventions is superior to routine care. Interventions encompass diet, cognitive training, physical activity, sleep, stress management, and adherence to medical treatment.
Method: In the COCOA study, cognitively impaired patients are randomly assigned to routine care or coaching plus routine care. Telephonic health coaching is provided by licensed dietitians, nutritionists and nurses. We monitor each participant for two years. In addition, COCOA evaluates "dense, dynamic data clouds (Price et al., 2017)" - consisting of clinical labs, lifestyle, genomic, proteomic, metabolomic and gut microbiome data for each participant - in an effort to explain the causal underpinning of any observed differences between the two arms. The methodology of this study has been previously used in the completed 100-Person Wellness Project (Price et al., 2017).
Result: As of June 2019, 53 participants are enrolled.
Conclusion: Enrollment and engagement of participants with prodromal AD in an intensive telephone based coaching trial with online cognitive training is challenging but feasible. Acquisition of dense data clouds permits interpretation of mechanisms underlying compliance and responses to interventions.

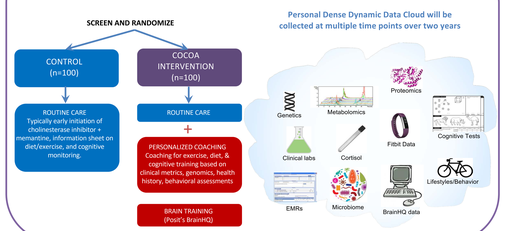
COCOA Coalition



PSJH ALZHEIMER'S PILLAR

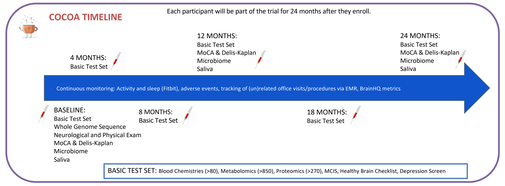
The Alzheimer's Translational Pillar is a collaboration of ISB and PSJH to advance systems biological understanding of Alzheimer's disease (AD). Our working hypothesis is that there are multiple causes of AD, and that the set of causes influencing AD initiation and progression in one individual may differ from the set of causes in another individual. We know that these causes include genetic components and we hypothesize that these causes include multiple environmental causes (e.g., trauma, infection, inflammation, toxins). These multiple causes lead to a complex disease. To ameliorate, treat, reverse, prevent, or delay AD therefore will likely require personalized and complex multimodal interventions. To advance the translational science of AD, we need to (1) better understand the genetic and environmental causes of AD, (2) understand the molecular consequences of these causes in the context of individuals, (3) develop multimodal therapies targeting both the underlying causes and symptoms of AD, (4) test these multimodal therapies in prospective trials, and (5) iterate. Iteration is important because we are not likely to design the best therapy at first. To enable iteration, trials must be fairly short. And trials must generate enough data so that enough knowledge is gained about the multimodal intervention that it can be intelligently tweaked for a next trial iteration. At ISB and other PSJH affiliates and collaborators, we are implementing projects spanning all aspects of this approach to understanding AD and developing and improving therapies for preventing, delaying, or reversing AD. These efforts include the PREVENTION Trial at the Pacific Neurosciences Institute and the COCOA Trial at Hoag.

Trial Design



COCOA TIMELINE

Each participant will be part of the trial for 24 months after they enroll.



Recruitment Progress

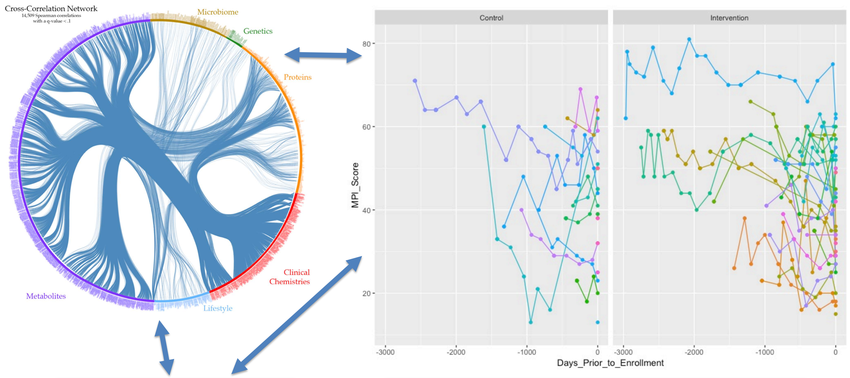
- IRB approved October 2017
- Recruitment began January 2018
- 53 participants recruited to date
- Goal: 200 participants

Inclusion Criteria

- FAST stage 2-4
- Age 50 and older
- Memory Performance Index ≤ 65
- English-fluent
- Existing medical conditions stable
- Computer and web-proficiency
- Ability to engage with coaches on telephone

Exclusion Criteria

- Other dementia disorder



COCOA ANALYSIS

The COCOA trial design has two separate, but related epistemological goals: (1) that of a prospective randomized controlled trial, with the null hypothesis that the two arms have equivalent responses to intervention if the interaction term between time and arm in a linear mixed-effect model is not significantly different from zero, and (2) to employ the rich array of epistemological analyses available when dense data (i.e., frequent measurements of many variables) are available. Furthermore, these personalized dense dynamic data (PDD) clouds enable analyses of coherence with existing systems biology networks that increasingly offer known or suspected causal or mechanistic relationships between molecular nodes in knowledge graphs. With these analyses we hope to:

- Identify markers that change over time due to intervention effects
- Leverage correlation networks (see Circos plot above) to identify physiological pathways associated with response to intervention
- Examine network perturbations that are associated with coaching and/or brain training
- Employ machine learning techniques to calculate disease risk scores and develop predictive classification models
- Apply atypical values analysis ("divergence") to discover individual-level markers that indicate pathways to disease or recovery

MECHANISTIC UNDERSTANDING OF TRAJECOTRY INFLECTIONS

This graph shows the trajectories in Memory Performance Index (MPI) of participants prior to enrollment in the COCOA Trial. Many participants had historical MCI Screening data, and these data were collected, with consent, as part of baseline enrollment. Some individuals in the trial had a longer history of historical screening than others; some enrolled individuals had no historical screening. All of these were done prior to intervention. Therefore, the sets of trajectories in both "Intervention" and "Control" facets of the above graph are drawn from the same enrollment population, and should show differences only due to random draw. Data after Day 0 would be expected to show differences in trajectory, if any, due to the intervention. We do not show this data here as we have not reached a formal trial analysis halting point.

These baseline trajectories show diversity in the cognitive abilities of the enrolled population at the time of enrollment (Day 0) as well as diversity in their MPI Score trajectories leading up to enrollment. Within each trajectory, there is moderate variability between measurements, and in some cases there are large deviations between measurements, possibly due to interventions (e.g., medication) received as part of routine care prior to the trial start date.

Our main analysis goal in the COCOA is to acquire two years of trajectory data on the MPI Score (one of our two primary endpoint variables), as well as on many other psychometric and molecular measurements. For each participating individual, we will have a quiver of these trajectories, from which to draw conclusions. Separately (see "Cross Correlation Network" to the upper right) we know the relationship of many of these variables from prior systems-biology network analyses, and for a subset of these pairs of relationships have some understanding of the causality and/or mechanistic of the those relationships. Incorporating prior knowledge of mechanism between pairs (or a greater number) of trajectories, plus time-dependencies, size of the effect, specificity of the effect, and other epistemological analyses may allow us to determine whether specific variables in the context of the COCOA trial are mechanistically related.

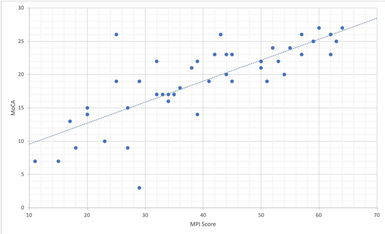
We advocate that all clinical trials should increasingly strive to incorporate dense longitudinal data acquisition as part of the basic trial design. Clinical trials should begin to identify the molecular details of causes of effects of interventions, not just relationships between an intervention and an effect. Such understanding allows intelligent improvement of interventions for future trials. Datasets become available for other meta-analyses, perhaps of very different subject domains than the current clinical trial. Much is given to clinical trials (funding, participant effort), so much is expected. Clinical trials must increasingly generate wider collateral value than to merely test a single null hypothesis. They must also advance basic understanding of biology and broader efforts in translational medicine.

AN UNCOMMON "COMMON SENSE" APPROACH TO KNOWLEDGE

Epistemology is innate. Humans start learning and building knowledge about their world as soon as they are born, and use a wide variety of inference tools as they age and learn. Generally speaking, they do a very good job of this and do it well. The set of tools for building scientific knowledge was outlined in 1965 by the English statistician Sir Austin Bradford Hill. These included methods for developing evidence based on significance (e.g., p-value), strength (e.g., effect size), consistency, time dependency, dose-response, coherence, plausibility, and replication. Unfortunately for 21st century science, shortly after Hill's criteria were laid out, 20th century statistics, logistics, and computational power drove the first two pillars of knowledge — significance and strength — so much to the forefront that they eclipsed all others elements of knowledge building for evidence-based medicine. Systems biology — to a large extent — is an effort to re-infuse all elements of epistemology back into medicine. Importantly, causality can only be determined through combined application of many of Hill's criteria. 20th-century evidence based medicine is rarely sufficient to determine causality and typically only in obvious circumstances, combining time dependency (e.g., taking a pill precedes getting better) with a p-value and an effect size. Building 21st century biological knowledge requires deployment of most of these criteria, particularly to build an understanding of causation. This is particularly true because the major problems facing us today — common complex diseases — are intractable to 20th century blunt force.

For Alzheimer's disease, it will be important to understand not just variables (such as APOE genotype and gender) that are correlated with phenotypes, but to understand how they cause these phenotypes. For COCOA — and for future translational medicine trials designed and sponsored by ISB & PSJH — we will therefore deploy not only the standard two Hill's Criteria (p-value/significance and strength), but also consistency, time dependency, coherence, dose-response, plausibility, replication, and other pillars of knowledge as they apply to particular efforts. Importantly, Hill's criteria emphasize experiment and falsifiability — classic elements of the scientific method. Systems biology prioritizes construction of network models (e.g., based on transcriptional regulatory networks) that include elements identified from genetic, epigenetic, RNAseq, and proteomics data and that identify key networks driving biological systems and responses. These networks are ideal resources for identification of remaining uncertainties, questions to be answered, and future experiments. Dose-response is also an important Hills criteria, but we must be careful in homeostatic and evolutionarily refined human systems, as often there is a "sweet point" for the effect of common alleles. Deep understanding of systems permits the rejection of Occam's razor (e.g., that all systems should be modeled linearly) in such cases. Many things are best in moderation — whether they are components of genome, diet, or lifestyle. We anticipate that the results of COCOA will identify systems that best promote wellness when they are activated neither too little nor too much.

Participants in COCOA will be assessed with the MCIS, which includes quantification of cognition with the Memory Performance Index (MPI) component score on a 0 to 100 scale (below normal: <50). The MPI will be our primary outcome measure for cognitive function. It is quick and inexpensive to administer. The MPI score is sensitive to slight cognitive deficits, and thus serves as an excellent single measure of cognition to serve as one of our two primary outcome measures (Shankle et al., 2009). Our other primary outcome measure is the Functional Assessment Staging Test (FAST) to evaluate overall disease progression. To inform executive function, participants will be evaluated by the Delis Kaplan Executive Function System (DK-EFS). DK-EFS consists of nine tests that produce 16 summary achievement scores. We will also collect metrics from BrainHQ cognitive training. MoCA will be collected to enable comparison with studies from other groups.



The MoCA and the MPI Scores are correlated. Each is subject to considerable variability, and is impacted by potentially unmeasured (or difficult to assess) factors such as mood and sleep. Some of these unmeasured factors account for some of the variability in the individual colored trajectories shown in the graph of MPI Score trajectories to the left.

Characteristic	Control (n=22)	Coaching (n=30)
Female, n	8 (36%)	10 (33%)
Age, mean years (range)	74.3 (58-89+)	75.4 (58-89+)
Enrollment MPI score, mean (range)	43.8 (20-64)	40.8 (17-63)
Race/ethnicity	22/22 white	27/30 white
BMI, mean (range), n=17	25.7 (19, 34)	24.9 (17, 237)
Blood draws completed (by May 2018):		
1	18	30
2	10	19
3	4	10
4	1	3
Baseline assessments completed	24	31
Microbiome data available	16	21
Maximum education completed		
High school/GED	2	2
Some college/tech school	1	7
Associate and/or bachelor's	10	11
Master's/doctorate/professional	5	7
Selected Clinical lab values:		
LDL Cholesterol, mg/dL, mean	117.3	106.4
HDL Cholesterol, mg/dL, mean	63.1	56.8
Total cholesterol, mg/dL, mean	201.3	183.2
Serum homocysteine, umol/L, mean	8.7	10.5
Hemoglobin A1C, %, mean	5.4	5.6
Glucose, mg/dL, mean	94.1	95.9

Baseline Characteristics of COCOA Participants

April 2/2	1
April 2/4	1
April 3/3	11
April 3/4	3
April 4/4	1

Coaching for Cognition in Alzheimer's (COCOA)

If you or someone you know is experiencing a decline in mental functioning due to Alzheimer's disease, you may qualify for a new clinical trial.

What is the Coaching for Cognition in Alzheimer's (COCOA) Study?

This is a study looking at the effects on mental functioning of both drug and lifestyle-based treatment. In addition, by collecting extensive data on both genetic and environmental factors, researchers hope to understand changes in the body that might predict changes in cognitive function. The COCOA study will look at how health coaching on these genetic, clinical and lifestyle factors might improve mental and function as well as overall quality of life when added to regular medical care.

What do I have to do if I take part in the COCOA study?

If you agree to participate, you will be followed for two years. During this two-year period, you will be asked to:

- Have a genetic assessment performed
- Have your mental and functional abilities assessed and complete lifestyle questionnaires up to 6 times
- Provide blood for measurement of a variety of clinical labs related to wellness and cognition up to 6 times
- Provide saliva for stress hormone measures and stool samples for a gut microbiome test up to 3 times
- Meet with a nutritionist, exercise specialist and health coach to work on lifestyle changes that might impact mental functioning.
- Participate in a specially designed online cognitive training program

You will be randomly assigned (like flipping a coin) to either the group receiving initial health coaching or a "control" group receiving regular medical care. If you are in the control group, you will still get all the standard medical care you would normally receive plus you will receive several months of health coaching on your lifestyle and lab results and the online cognitive training at the end of the two-year study. There is no cost to you to participate in the study and your insurance company won't be charged for study-related procedures.

Who can participate in the COCOA study?

You may qualify if you are:

- Age 50 and older (no age upper limit)
- Experiencing an early stage mental impairment.
- Experiencing an early stage functional loss.
- Proficient in spoken and written English.

How can I participate in the COCOA study?

Please contact the Hoag study coordinators to learn more and to schedule your first visit.

Laura Heim, RN 949-764-8180
Sheree Phillips 949-764-7280

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COCOA Study Team
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For further information please visit our website Hoag.org/Neurosciences or contact us by email: jared.roach@systemsbiology.org

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