Development of Novel Biomarkers for Early Detection of Executive Function Deficits

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SPECIFIC AIMS

The overarching goal of this R03 small research project is to develop and validate novel biomarkers for the early detection of executive function deficits in children aged 5-7 years. This project will leverage existing neuroimaging and behavioral data from the Cognitive Development Study to identify neural signatures that predict later development of cognitive control difficulties.

Specific Aim 1: Identify candidate neural biomarkers associated with executive function performance in young children. We will analyze existing fMRI data from 120 children who completed a child-friendly executive function task battery at ages 5-7. Using machine learning approaches, we will extract neural features that are most predictive of concurrent performance on standardized executive function measures.

Specific Aim 2: Validate the predictive utility of identified biomarkers for future executive function outcomes. We will test whether the neural signatures identified in Aim 1 predict executive function performance and real-world outcomes (academic achievement, behavioral regulation) at 2-year follow-up assessments.

Impact: This R03 project will deliver a set of validated neural biomarkers with potential for early identification of children at risk for executive function difficulties. These findings will form the foundation for a future R01 application focused on developing and testing targeted early interventions for these at-risk children.

RESEARCH STRATEGY

Significance

Executive function deficits are implicated in multiple neurodevelopmental disorders and predict academic and behavioral difficulties. However, reliable early detection remains challenging, as these skills develop rapidly during early childhood and standard behavioral assessments often lack sensitivity in young children. Identifying objective neural biomarkers could enable earlier and more precise identification of children who would benefit from intervention.

This project addresses a significant gap in developmental cognitive neuroscience by leveraging an existing, well-characterized dataset to develop biomarkers that can be applied in future research and clinical settings. The project's focus on ages 5-7 years is strategic, as this represents a critical period of executive function development and a time when early intervention may be most effective.

Innovation

This R03 project is innovative in several ways:

1. It repurposes existing neuroimaging data from a developmental cohort to answer new questions about biomarkers of executive function, maximizing the scientific yield from prior research investments.
2. It employs advanced machine learning techniques specifically optimized for pediatric neuroimaging data, addressing unique challenges such as higher motion artifacts and developmental variability.
3. It focuses on biomarker development at ages 5-7, earlier than most existing research, creating opportunities for earlier identification and intervention.

Approach

Data Source: We will utilize existing data from the Cognitive Development Study, which includes structural and functional MRI, diffusion tensor imaging, and comprehensive neurocognitive assessments from 120 children (ages 5-7 at baseline) with 2-year follow-up data available.

Aim 1 Methods: We will extract features from task-based fMRI during three executive function tasks (inhibitory control, working memory, cognitive flexibility). Features will include activation patterns, connectivity metrics, and network properties. We will apply elastic net regression and random forest algorithms to identify the neural features most predictive of concurrent executive function performance.

Aim 2 Methods: We will test whether the biomarkers identified in Aim 1 predict executive function performance and real-world outcomes at the 2-year follow-up. We will use multiple regression models controlling for age, sex, socioeconomic status, and baseline performance.

Statistical Power: Based on prior work, our sample size of 120 provides >80% power to detect medium effect sizes ($r = 0.25$) at $\alpha = 0.05$ after correction for multiple comparisons.

Timeline: This project is designed for completion within the 2-year R03 timeframe, with Year 1 dedicated to Aim 1 analyses and Year 2 focused on Aim 2 validation and preparation of manuscripts and the subsequent R01 application.

BIBLIOGRAPHY & REFERENCES CITED

Bibliography

BUDGET & JUSTIFICATION

This five-year R01 project requires the following resources to accomplish the proposed aims:

PERSONNEL

Principal Investigator (Dr. Jane Smith, 25% effort): Dr. Smith will provide overall scientific leadership for the project, oversee all aspects of study design, data collection, analysis, and dissemination. She will supervise research staff and ensure adherence to timelines and research protocols.

Co-Investigator (Dr. Robert Johnson, 15% effort): Dr. Johnson will contribute expertise in neuroimaging methods and analysis, assist with fMRI protocol development, and supervise the neuroimaging data processing pipeline.

Co-Investigator (Dr. Sarah Williams, 10% effort): Dr. Williams will contribute expertise in developmental psychopathology, assist with clinical assessments, and help interpret findings in the context of neurodevelopmental disorders.

Postdoctoral Researchers (2 FTE): Two postdoctoral researchers will coordinate data collection, implement preprocessing and analysis pipelines, conduct statistical analyses, and prepare manuscripts and presentations.

Research Assistants (2 FTE): Two research assistants will recruit and schedule participants, administer cognitive and clinical assessments, assist with neuroimaging data collection, and manage research databases.

MRI Technician (25% effort): A certified MRI technician will operate the MRI scanner during data collection and ensure high-quality neuroimaging data.

EQUIPMENT

EEG System Upgrade ($75,000, Year 1 only): Funds are requested to upgrade the existing EEG system to enable simultaneous fMRI-EEG recording. This includes MRI-compatible caps, amplifiers, and software.

Computing Cluster Expansion ($50,000, Year 1 only): Additional computing nodes are needed for the intensive computational modeling and machine learning analyses proposed in Aims 2 and 3.

SUPPLIES

Neuroimaging Supplies ($15,000/year): Includes MRI-compatible response devices, head cushions, disposable EEG electrodes, and participant monitoring equipment.

Computing Supplies ($10,000/year): Storage media, backup systems, software licenses, and computing peripherals.

Office Supplies ($5,000/year): General office supplies, printing costs for assessment materials, and participant recruitment materials.

TRAVEL

Conference Travel ($15,000/year): Funds for PI, co-investigators, and postdocs to attend and present at 2-3 major conferences per year (e.g., Organization for Human Brain Mapping, Society for Neuroscience, Cognitive Neuroscience Society).

Collaboration Travel ($5,000/year): Travel for PI and key personnel to meet with collaborators for specialized training and data analysis.

PARTICIPANT COSTS

Participant Compensation ($60,000/year): Compensation for 180 participants (60 per group) at $250 per participant for approximately 6 hours of testing (includes neuroimaging, cognitive assessments, and clinical interviews) plus travel expenses. Additional funds for follow-up testing in years 3-5.

Participant Recruitment ($10,000/year): Advertising costs, community outreach materials, and screening expenses.

OTHER DIRECT COSTS

MRI Scanner Time ($120,000/year): 300 hours of scanner time per year at $400/hour for participant scanning and pilot testing.

Publication Costs ($10,000/year): Open access publication fees for approximately 4-5 manuscripts per year.

Research Computing Services ($15,000/year): High-performance computing resources and technical support for computational modeling and large-scale data analysis.

BUDGET JUSTIFICATION SUMMARY

The requested budget is appropriate and necessary to complete the proposed research. Personnel costs reflect the interdisciplinary expertise required for this complex project involving clinical populations, advanced neuroimaging methods, and sophisticated computational analyses. Equipment costs are essential for the simultaneous fMRI-EEG recording central to our approach. Participant costs reflect the comprehensive assessments and the need to adequately compensate families for their substantial time commitment. Neuroimaging costs are based on current rates at our institution's imaging center. This budget has been carefully planned to ensure the most efficient use of resources while enabling the successful completion of all aims.