
MotherToBaby


OTIS
Organization of Teratology
Information Specialists

Designing And Executing Neurobehavioral Assessment Batteries in Longitudinal Studies of Exposure

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OBJECTIVES

Describe main principles in designing neurobehavioral test batteries including:

- Age
- Accuracy
- Administration method
- Time and child state
- Staffing, training, blinding
- Covariates & Potential Confounders

Other Considerations

- Clinical relevance & reporting results
- Pilot testing

Growth

Health

Disease

NEUROBEHAVIOR

Cognition

Motor Development

Behavior

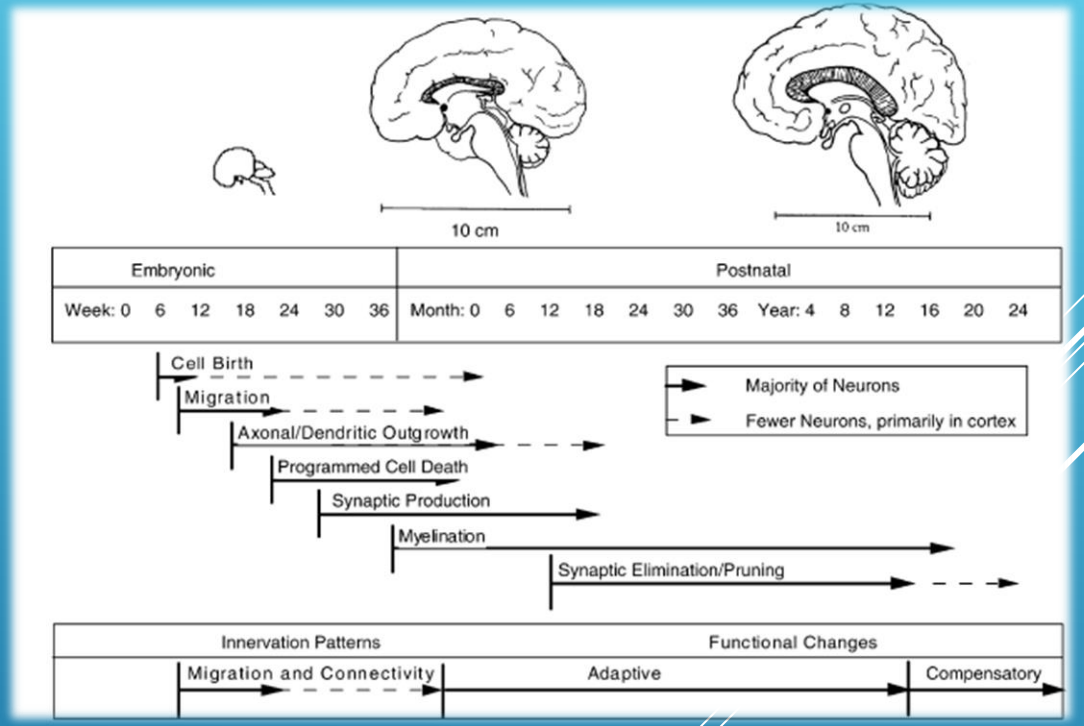
Socialization

Achievement

BENEFITS OF LONGITUDINAL COHORTS

ENDLESS OUTCOMES TO STUDY

- Capture exposures and outcomes across the lifespan
  - Patterns, trajectories, vulnerable periods, delayed neurotoxicity



Andersen 2003 Neuroscience and Biobehavioral Reviews

BENEFITS OF LONGITUDINAL COHORTS

LIFESPAN FOCUS

HEALTH OUTCOMES AND MEASURES OF THE ENVIRONMENT (HOME) STUDY

- Primary Objective: To improve our understanding of the impact of exposures to ***common environmental toxicants*** on infant and child ***health, development, and behaviors*** using a pregnancy and birth cohort
- Observational study with nested randomized intervention trial to reduce lead exposure and home injury
- Pregnant women (N=468) enrolled 2003-2006
- Offspring (N=441) have been followed from birth to age 18 years

Braun 2017 Int'l J Epidemiology, Braun 2020 BMJ Open
https://homestudy.research.cchmc.org

DETAILED EXPOSURE MEASUREMENT

Common Environmental Toxicants

- Air pollution
- Flame retardants (PBDEs, OPEs)
- Fluoride
- Metals – Lead, Arsenic, Cadmium, Mercury
- Tobacco (cotinine)
- PCBs
- Perfluoroalkyl substances chemicals
- Pesticides (OPs, OCs, pyrethroids)
- Phenols, Triclosan
- Phthalates

Environmental Samples

- House dust (wipes)
- House dust (vacuum)
- Soil
- Water

Biological Samples

- Blood
- Urine
- Hair
- Meconium
- Stool
- Saliva & Buccal cells
- Teeth
- Toenails
- Vernix (subsample - 122 newborns)

OUTCOMES: HEALTH & NEUROBEHAVIOR

- **Growth**
  - Medical chart at birth
  - Measured by staff at study visits
  - Puberty – self-assessed
- **Respiratory Health**
  - Survey
  - Spirometry
  - Exhaled NO
- **Cardiometabolic Health**
  - Laboratory assays
  - BP measurement
- **Adiposity & Bone Health**
  - Ht, wt, circumferences measured
  - DXA scan

- **Neurobehavior**
  - Caregiver report
  - Direct assessment by trained research staff
  - Child self-report
- **Mental Health**
  - Survey of caregiver
  - Survey of child
- **MRI**
  - Dedicated research MRI

- Multiple repeated measures
- Rich covariate dataset

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL MEASURES

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL MEASURES
AGE

- Outcomes should be relevant to child age over course of study
  - Infancy
  - Early Childhood
  - Preschool
  - School Age
  - Adolescence
  - Young adulthood

HOME Study visits
Prenatal
Birth & 4 weeks
1, 2, 3 years
4, 5 years
8 years
12 years
18 years

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL MEASURES
ACCURACY

- Outcomes should be relevant to child **age** over course of study
- Accuracy
  - Sensitivity & Specificity
  - Predictive of future outcomes
    - Improves with age/development

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL ASSESSMENTS ADMINISTRATION METHOD

- Outcomes should be relevant to child age over course of study
- Accuracy
- Administration method
  - Caregiver survey vs Direct administration
  - Outcome specific
  - Balanced blend

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL ASSESSMENTS
TIME & CHILD FACTORS

- Outcomes should be relevant to child age over course of study
- Sensitivity and specificity
- Administration method
- Time and child state

HOME Study Visit Lengths						
Age	Birth/4w	1,2,3y	4,5y	8y	12y	18y
Visit Length	30m	2-3h	3-4h	3-4h	7-8h	3-6h*

***Multiple visits**

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL ASSESSMENTS STAFFING

- Outcomes should be relevant to child age over course of study
- Accuracy
- Administration method
- Time and child state
- Staffing, training, blinding

HOME Study Visit Staffing						
Age	Birth/4w	1,2,3y	4,5y	8y	12y	18y
Staff *	4	2	2	2-3	2-3	2-3

***Some turnover**

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL ASSESSMENTS COVARIATES

- Outcomes should be relevant to child age over course of study
- Accuracy
- Administration method
- Time and child state
- Staffing, training, blinding
- Covariates & Potential Confounders
  - Relevant to exposures
  - Relevant to outcomes
  - Relevant to developmental stage
  - Survey, chart review, assessment, address

Key Covariates added:
Demographics
L&D events
Gestational age, bw
Drug/alcohol use

Construct	Instruments	Format	Setting
Newborn Neurobehavior	NICU Network Neurobehavioral Scale (NNNS)	Direct administration	Hospital before d/c Home @ 4-5w

NEUROBEHAVIORAL TEST BATTERY NEWBORN

Considerations:
Snapshot of newborn TODAY
Examiner qualifications
Training burden
Location & timing

HOME Study

CONSIDERATIONS FOR SELECTING NEUROBEHAVIORAL ASSESSMENTS
STAFF TRAINING & QC

- Heavy training burden for some direct assessment measures
- Trainees need dedicated time and access to a similar population for adequate practice
  - Investigators and staff need to understand the importance of proper training and accurate assessment
  - Study should not launch until training is completed
- Frequency and process of rechecks
  - Form and scoring review
  - Video review or live observation

Key Covariates added:
Caregiver IQ
Home environment
Caregiver depression*
Parenting stress

Construct	Instruments	Format	Setting
Cognitive & Motor Development	Bayley Scales	Direct administration	Clinic/Laboratory
Internalizing & Externalizing Behavior	Behavior Assessment System for Children (BASC)*	Caregiver survey	Flexible
Executive Function	Brief Rating Inventory of Executive Function (BRIEF)*	Caregiver survey	Flexible
Sleep	Children's Sleep Habits Q*	Caregiver survey	Flexible

*** These measures repeated at future study visits**

NEUROBEHAVIORAL TEST BATTERY EARLY CHILDHOOD – AGE 1,2,3Y

Considerations:
Examiner qualifications
Training burden
Caregiver present

HOME Study

CHILD DEVELOPMENT ASSESSMENT COMPARISON

	Bayley Scales -4	Ages & Stages Questionnaire
Administration	Direct administration in lab	Caregiver screener survey
Time	90 minutes	15 minutes
Costs		
Supplies and forms	$14/participant	None
Scoring subscription	$55/year	$150/year
Training costs	$405/examiner	None
Training burden	3-6 months	None
Ongoing QC	Annual rechecks	None
Post visit processing	Data extraction	Data extraction
Referral value	Valid clinical cut-offs	Screener – refer for more testing

Key Covariates added:
Caregiver ADHD (CAARS)
Caregiver SCL90-R*

Construct	Instruments	Format	Setting
Language Development	CELF-P	Direct administration	Clinic/Laboratory
Executive Function	Shape School, TRAILS-P	Direct administration	Clinic/Laboratory
Visuospatial Processing	NEPSY tower, design copying, block construction	Direct administration	Clinic/Laboratory
Attention & Response Inhibition	K-Conners	Computer administration	Clinic/Laboratory
Intelligence	WPPSI (5y)	Direct administration	Clinic/Laboratory
Reading Readiness	Woodcock-Johnson (5y)	Direct administration	Clinic/Laboratory

NEUROBEHAVIORAL TEST BATTERY PRESCHOOL - AGE 4&5Y

HOME Study

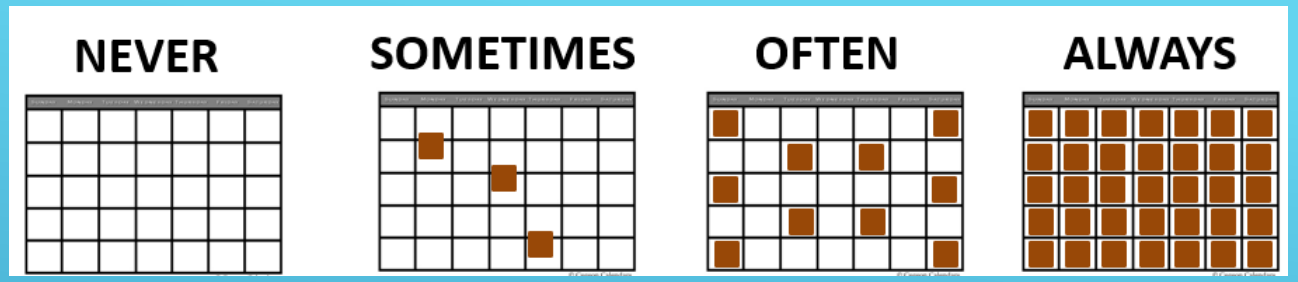
Considerations:
Longer study visits
Serial results
Caregiver not present

Construct	Instruments	Format	Setting
Intelligence	WISC	Direct administration	Clinic/Laboratory
Reading & Math Achievement	WRAT	Direct administration	Clinic/Laboratory
Attention & Response Inhibition	Conners	Computer administration	Clinic/Laboratory
Visuospatial Processing & Memory	Virtual water maze	Computer administration	Clinic/Laboratory
Depression	Children's Depression Inventory	Self-report survey	Clinic/Laboratory
Anxiety	Spence or SCARED	Self-report survey	Clinic/Laboratory

NEUROBEHAVIORAL TEST BATTERY SCHOOL AGE - AGE 8Y

HOME Study

Considerations:
Functional impairments
Able to self-report



Construct	Instruments	Format	Setting
Intelligence	WISC	Direct administration	Clinic/Laboratory
Reading & Math Achievement	WRAT	Direct administration	Clinic/Laboratory
Attention & Response Inhibition	Conners	Computer administration	Clinic/Laboratory
Visuospatial Processing & Memory	Virtual water maze	Computer administration	Clinic/Laboratory
Depression	Children's Depression Inventory*	Self-report survey	Clinic/Laboratory
Anxiety	Spence or SCARED	Self-report survey	Clinic/Laboratory

NEUROBEHAVIORAL TEST BATTERY SCHOOL AGE - AGE 8Y

HOME Study

* Depression intervention & referral as needed

Participants costs:
$2800 each w/MRI

Key Covariates added:
Urine Drug screen
Pubertal staging
Parenting relationship
Diet & Physical activity

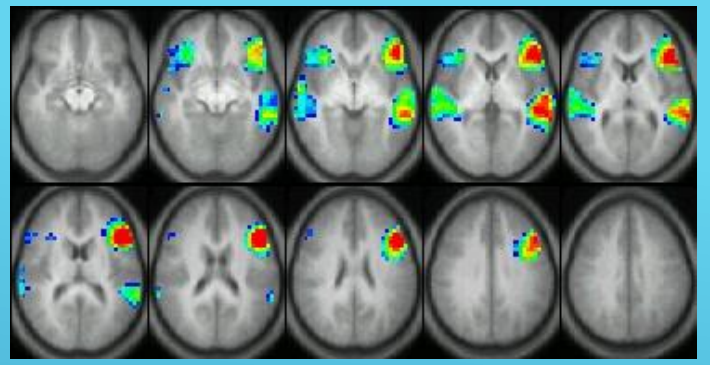
Construct	Instruments	Format	Setting
Depression	Children's Depression Inventory	Self-report survey	Clinic/Laboratory*
Anxiety	Spence or SCARED	Self-report survey	Clinic/Laboratory
Social Skills	SSiS		Clinic/Laboratory
Memory	ChAMP	Direct administration	Clinic/Laboratory
Brain Structure, Organization, Function	MRI, MRS, DTI, fMRI	MRI scanner	Imaging Center

NEUROBEHAVIORAL TEST BATTERY ADOLESCENCE - AGE 12Y

HOME Study

Considerations:
Strengths & deficits more predictive

Participants costs:
$1800 each w/MRI



Construct	Instruments	Format	Setting
Intelligence	WASI	Direct administration	Clinic/Laboratory
Depression	Beck Depression Inventory	On-line	Clinic/Laboratory*
Anxiety	SCAARED	REDCap	Flexible
Stress	Perceived Stress Scale	REDCap	Flexible
Delinquency, Risk Behaviors	YRBS	REDCap	Flexible
Brain Structure, Organization, Function	MRI, MRS, fMRI	MRI scanner	Imaging Center

NEUROBEHAVIORAL TEST BATTERY YOUNG ADULTHOOD - AGE 18Y

HOME Study

Considerations:
Full range of impact

OTHER CONSIDERATIONS
CLINICAL RELEVANCE & REPORTING RESULTS

- Outcomes should be relevant to child age over course of study
- Accuracy
- Administration method
- Time and child state
- Staffing, training, blinding
- Covariates & Potential Confounders
- Clinical relevance & reporting results
  - Assistance with access to services
  - Ethical obligations
  - Participant requests for information

OTHER CONSIDERATIONS
CLINICAL RELEVANCE & REPORTING RESULTS

- **Incidental Findings**
  - Unexpected
  - Beyond the study aims
  - Potentially clinically relevant

  - Establish a priori cut-offs for development and behavior testing
  - Suicide screening for elevated depression

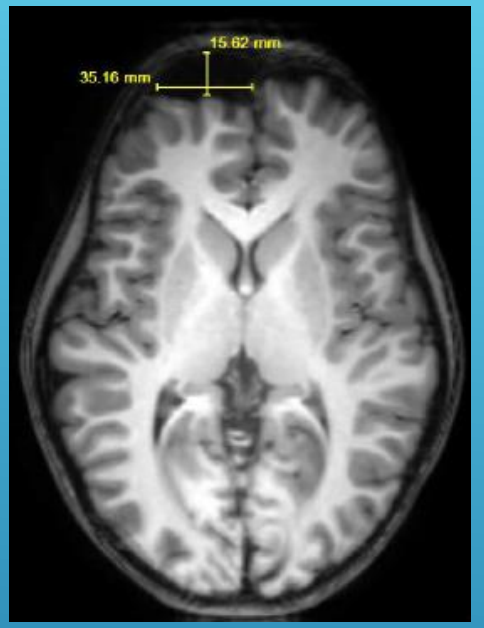
- **Report to …**
  - Primary caregiver for minors
  - Study participant (≥18y)
  - Primary Care Provider with permission

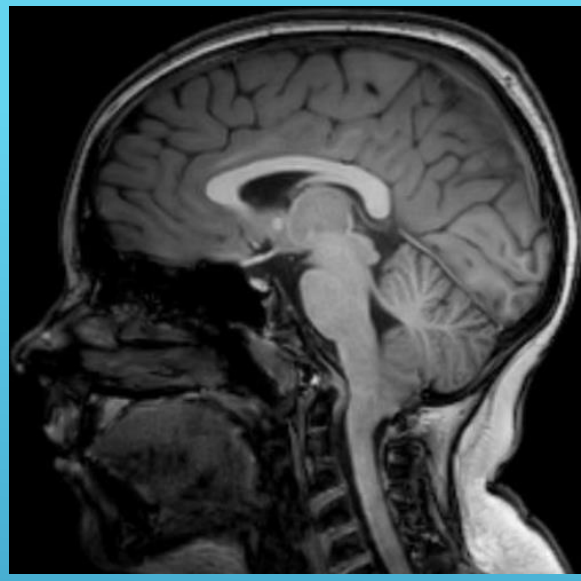
OTHER CONSIDERATIONS
CLINICAL RELEVANCE & REPORTING RESULTS

Incidental findings unrelated to study aims

- 6.5% (12/186) @ age 12y
- 4.2% (11/261) @ age 18y

- Phone call to caregiver/participant
- Referral to primary care physician
- Clinical MRI





This letter is regarding your patient, ***Name*** *(**DOB: xx/xx/xxxx**)*. Name and her family are enrolled in the HOME Study, through Cincinnati Children's Hospital. Included in the study protocols are regular assessments of child development and behavior. At the request of Name mother, this letter is intended to inform you of the results of the most recent assessments. Permission to release this information to your office was granted by Name mother in person on xx/xx/xxxx, and by phone on xx/xx/xxxx.

Name x years of assessments in the study are summarized in the following tables.

Assessment	12 Month Visit xx/xx/xxxx xx months	24 Month Visit xx/xx/xxxx xx months	36 Month Visit xx/xx/xxxx xx months	48 Month Visit xx/xx/xxxx xx months
Bayley Mental (MDI)				
Chronological				
Developmental Age				
Bayley Motor (PDI)				
Chronological				
Developmental Age				
BASC2				
BRIEF-P				
SRS				

48 Month - Clinical Evaluation of Language Fundamentals – Preschool – (CELF-P-2)
Completed on xx/xx/xxxx at xx months

Core and Indexes	Standard Score
Core Language Score (CLS)	
Receptive Language Index (RLI)	
Expressive Language Index (ELI)	
Language Content Index (LCI)	
Language Structure Index (LSI)	

OTHER CONSIDERATIONS
CLINICAL RELEVANCE & REPORTING RESULTS

- At participant request

Child's Name: xxx
Date of Visit: xx/xx/xxxx Age at Visit: 7 years 10 months

Wechsler Intelligence Scale for Children – IV (WISC-IV)

Scale	Composite Score (IQ)	Percentile Rank	Qualitative Description
Verbal Comprehension	116	86	High Average
Perceptual Reasoning	112	79	High Average
Working Memory	104	61	Average
Processing Speed	85	16	Low Average
Full Scale	109	73	Average

Wide Range Achievement Test – 4 (WRAT-4)

Subtest	Scaled Score	Percentile Rank	Grade Equivalent
Word Reading	111	77	4.8
Sentence Comprehension	120	91	5.5
Math Computation	109	73	4.0
Reading Composite	116	86	NA

OTHER CONSIDERATIONS
CLINICAL RELEVANCE & REPORTING RESULTS

OTHER CONSIDERATIONS
PILOT TESTING

- Organizing and scheduling
- Consenting process
- Refine questionnaires and interviews
- Environmental and biological sample collection
- Staff training on assessments
- Collaboration with other services
- Visit flow
- Data capture and management
- Create a pilot test participant pool to continue through the study duration
- **BUILD PILOTS INTO THE BUDGET!!**

FINAL THOUGHTS

- Plan carefully
- Consult with experts
- Learn as you go
- Pilot testing is essential
- Funding – Cohort studies are very expensive

Funding for Active Data Collection

P01ES011261	R01ES027224
R01ES014575	R01ES025214
R01ES020349	R01ES028277
R01ES033252	R01ES030078
R01ES031621	R00ES034086

FAMRI CIA award

ACKNOWLEDGEMENTS

- HOME Study Participants, Investigators, and Staff

- References:

  - Andersen (2003) Neuroscience and Biobehavioral Reviews
  - Booth (2010) The British Journal of Neuroradiology
  - Dietrich et al. (2005) Environmental Health Perspectives
  - Wilfond & Carpenter (2008) Journal of Law, Medicine, & Ethics
  - Adobe Stock images

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