Translating basic behavioral science into clinical interventions for childhood obesity

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Translational Research

- Bench to bedside
- Bridge gap between basic and clinical sciences
- Move knowledge and methods across levels of analysis
Why is translational research a challenge for behavioral sciences

- In drug development, the industry employs scientists to review new developments in basic science that can lead to new drugs.

- Behavioral science does not have an industry developing products.
  - It is up to clinical investigators to read basic science to keep up with new discoveries, or
  - Basic scientists need to learn clinical methods to apply their knowledge, or
  - Basic and clinical scientists need to work together in multidisciplinary teams.
Normal science or paradigm shifts

- Translational research can move across levels of analysis in normal science or paradigm shifts
  - Normal science represents systematic replication across levels of analysis
  - Paradigm shifting science represents a new paradigmatic approach to a problem

- Creativity is needed for both normal and paradigm shifting approaches to translation research
  - Examples from incubator and GPS research
Topics to be addressed

- Brief review of 2 examples from my research on translational research
  - Basic science of choice led to research on increasing physical activity
  - Basic science of behavioral genetics led to studying gene concordance in family-based behavioral treatment of pediatric obesity

- Discuss barriers to translational research
Experimental Design: Alcohol Dependence

- Rats randomized to control, intermittent free choice (once per week), continuous free choice, or forced intake of ethanol
- Became dependent on ethanol over 32 weeks of drug administration
- Animals kept ethanol-abstinent for 3 months, during which time they showed withdrawal (change in pain threshold, hyperthermia, inactivity)
- Animals then provided self-administration test

Experimental Design: Opiate Dependence

- Rats randomized to control, choice or forced intake of etonitazene
- Became dependent on opiate over 30 weeks of drug administration
- Animals kept opiate-abstinent for 19 weeks, during which time they showed withdrawal (change in pain threshold)
- Animals then provided self-administration test

It could be worse for your heart than cholesterol.
Effects of decreasing sedentary behavior versus increasing activity on weight change in obese children

- Obese 8-12 year-old children from 61 families randomized to groups that targeted:
  - Increased physical activity
  - Decreased sedentary behavior
  - Combined increased physical activity, decreased sedentary behavior

- Provided 4 month intensive treatment, followed at 12 month post randomization
Pediatric Weight Control

- Family-based weight control is an evidence based treatment for pediatric obesity
  - Over 30 years of research on Family-Based Treatment (FBT)
    » Including the parent as an active participant in treatment improve long-term (10 year) outcome for the child
    » Lifestyle intervention is associated with superior long-term outcome than programmed aerobic exercise
Long-term effects of treating the parent + child

Long-term effects of lifestyle exercise, aerobic exercise and calisthenics

Parent-child weight loss in family-based weight control

- One of the most reliable changes in family-based weight control is the strong relationship between parent and child weight loss.

- Having a successful parent is a strong predictor of child success.
  - Observed in our very first FBT study and replicated many times since.
  - Usual correlation between parent and child weight loss between $r = 0.40$ to $0.60$. 
Mechanisms for similarity in parent/child weight loss

- Behavioral mechanisms include:
  - Modeling, as parents who lose weight are models for child behavior change, and children and parent both report modeling is a factor related to weight loss
  - Shared family environment that influences both parent and child in the same way

- Behavioral genetic mechanisms include
  - Common genetic predisposition to respond to environmental changes in the same way
  - Must be mediated by common behavioral phenotypes
Reinforcing value of food

- 1000’s of studies have used food as a reinforcer to understand basic mechanisms of learning and the neurobiology of reinforcement.

- Subjects who find food more reinforcing consume more food in ad lib eating situations (Epstein et al, 2004).

- Food is more reinforcing for obese vs. non-obese subjects (Saelens and Epstein, 1996, Temple et al, 2008).

- Food reinforcement phenotype reliable (test-retest r > .80).

- Reinforcing value sensitizes over time for obese subjects (Temple et al, 2009, Clark et al, 2010).

- Food reinforcement predicts weight gain
  - Lean children who find food more reinforcing gain more weight than lean children who do not find food as reinforcing (Wardle et al, 2009).

- The reinforcing value of food is a shared behavioral phenotype (Epstein et al, 2008).
Dopamine

- Dopamine modulates the reward value of food, drink, sexual behavior, social reinforcers, and drugs of abuse (Berridge & Robinson 1998; Martel 1996).
- Dopamine genetics influence the release, reuptake, and receptor binding determine brain dopamine activity.
- Reduced dopamine binding to D2 receptors may be associated with addictive behaviors, increased eating, and obesity (Wang, Volkow et al 2001; Epstein et al 2002).
Research Question

- Is it possible that the similarity in parent-child weight loss is due to common genes that predispose the parent and child to respond to a standard treatment in the same way?
  - Particularly the D2 gene that is related to food reinforcement, that is a shared behavioral phenotype.
Does concordance of parent/child genes relate to similarity of weight loss?

- 26 families with obese parents and obese 8-12 year-old children who participated in standard FBT were studied.
- Families were coded as to whether the parent and child had the same number of DRD2 A1 alleles (0, 1 or 2).
- Regression models were run with gene concordance as a predictor of the relationship between parent and child zBMI change.
Does concordance of parent/child genes relate to similarity of weight loss?

- The correlations between child and parent zBMI changes at 6 and 12 months were 0.69 and 0.77.

- Relationship between parent and child zBMI changes:
  - If concordant, parent/child relationships of 0.78 and 0.89 ($\beta = 0.93$ and 1.01, p’s < 0.001)
  - If discordant, parent/child relationships of 0.59 and 0.24 ($\beta = 0.28$ and 0.22, p’s > 0.05)

- If parents were at least moderately successful in weight loss and the parent and child were concordant for the Taq1 A1 allele
  - Children showed 2X ZBMI change at six months (-.352 vs -.175) and >4X change at twelve months (-.466 vs -.109).
Does concordance of parent/child genes relate to similarity of weight loss?

Change at 6 Months

Change at 12 Months

**Graphs showing concordance and discordance of Taq1 A1 alleles:**
- **Discordant for Taq1 A1 alleles**
- **Concordant for Taq1 A1 alleles**

**Axes:**
- **X-axis:** Parent 0-6 zBMI Change
- **Y-axis:** Child zBMI Change

The graphs illustrate the relationship between parent and child BMI changes and the concordance of Taq1 A1 alleles at 6 and 12 months.
Variables important in my bridging gap between basic and clinical research

- I am very interested in basic science and read a lot of basic science
  - While I read clinical research, my ideas for new interventions often come from basic science
    » Need to become selective reader 😊

- I conduct both basic research and clinical research
  - I have learned enough basic science or have colleagues who provide the basic science expertise

- I have had success in adapting basic science ideas and paradigms into clinical research
Challenges in translational research I

- Graduate school training is very insular and laboratory specific for many people
  - Students are not often encouraged to work with many people in a multidisciplinary or interdisciplinary environment

- Biases may exist across levels of analysis that push people away from working at higher levels of analysis
  - Bottom up science favors lower levels of analysis
  - There is a certain “snottiness” for the more basic the better
  - These schisms can run very deep, which has led to departmental separations and evolution of behavioral neuroscience outside of psychology departments
Challenges in translational research II

- Lack of interest/expertise in basic science and/or lack of basic science colleagues

- Difficulties in getting basic and clinical scientists to work together
  - Examples of creativity (Pixar, Apple) work because they are not linear production models, but engage all members of the team in the act of creativity and problem solving
  - Translational science often uses a more linear model in which a scientist at a higher level of analysis is using a paradigm or method developed by a more basic scientist, but they are not working together
EARTH MOON TRANSIT
DISTANCE VS DIMENSIONAL RELATIVITY

[Graph showing Earth and Moon transit with a curve indicating distance change]
Challenges in translational research III

- It may be hard to reinforce people for working together
  - Who gets credit?
  - How are promotion and tenure decisions are made?
  - Do departments and schools value multidisciplinary collaboration?

- Universities usually don’t provide resources for extended multidisciplinary collaborations that stimulate translational science
  - Meeting times
  - Are seed monies available to develop collaborations?
  - Example of Pixar suggests trust needs to be developed, and the team needs to work together for extended periods to maximize creativity and productivity
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