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Child and Adolescent Mental Health

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The value of experience is not in seeing much, but in seeing wisely.—William Osler

This second issue of the Colorado Journal of Psychiatry and Psychology takes us into the depths of a vibrant academic pediatric mental health program. Topics covered include research (translational neuroscience; Calvin et al, Wei et al), the challenges of being an early-career faculty member at a large medical university and major children's hospital (Germone et al), forging new approaches to designing clinical services (Kelly et al, Towhy et al), and the details of clinical practice (Patel et al, Kaur et al).

As our most-respected international mental health journals have appropriately turned their attention to disseminating the best science, we rarely see such a mix of papers. And while through this approach we gain invaluable insights into the science of our field, what we lose out on is a publication that serves as an accurate reflection of the day-to-day realities of an academic mental health program. That is not the case in this issue of the Journal.

These papers, written by our faculty and trainees, serve to ground us in these realities, and remind us that excellence in research, service development, and clinical care are inextricably linked, making this issue of the Journal an enlightening and important read.

– *Douglas Novins*

This issue is dedicated to the memory of Professor Randy Ross, who passed away as this issue was coming to press. Randy was an intellectual leader of our extensive developmental research portfolio at the University of Colorado and a highly-respected scientist. Please see Randy's biosketch on page 90 and the full text of this dedication on page 93.

School of Medicine
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Editorial Staff

Call for Papers on Children's Mental Health

The *Colorado Journal of Psychiatry and Psychology* will again be accepting papers with a focus on child and adolescent mental health for an issue to be published in 2017. A more detailed call for papers will be posted on the Journal website in early 2017.

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Working Together: Collaboration in Academic Pediatric Mental Health

From the Editorial Staff: Marissa Schiel, MD, PhD; Emily Edlynn, PhD

We are thrilled to complete this second issue of the *Colorado Journal of Psychiatry and Psychology.* As we reflected on our collection of articles, we realized that a central theme of this issue is collaboration across disciplines and levels of training. Collaboration touched every aspect of this issue, from the editorial team's composition, to the diverse representation among reviewers and authors, and to the content of the articles themselves, covering clinical practice, research, training, and professional development. We believe the breadth and depth of this collaboration enriches the quality of work presented and makes the Journal more meaningful to readers with a variety of backgrounds and experiences.

Multidisciplinary collaboration is not a new concept and has long been hailed as the standard of care, despite the real-world challenges of providing true multidisciplinary care (eg, cost, infrastructure).1 This longstanding emphasis is taking on new urgency, however, in our shifting health care system, which is in a slow-burning crisis of inefficient systems and increasing costs. As assessment and modification of health care services become central to justifying interventions, reducing costs, and improving health outcomes, the importance of integrating behavioral health with traditional medical care has gained traction. For example, the Centers for Medicare and Medicaid Services (CMS) has recently proposed a "psychiatric Collaborative Care Model" that would provide coverage for an integrated team of a primary care physician, behavioral health care manager, and consulting psychiatrist.2 This commendable step forward demonstrates progress in recognizing the critical link between behavioral and physical health3 as well as between behavioral health providers of different disciplines.

In this issue of the Journal, Kelly et al survey multidisciplinary transplant treatment team members on their perceptions of medical adherence in adolescents post-transplant, which underscores the importance of collaboration among the medical and behavioral health providers of these teams as they strive to improve care for their complex patients. The 2 case studies by Patel and Sanner, and Kaur et al further elucidate the significance and compounded value of involving multiple disciplines and types of interventions to achieve positive outcomes for very complicated clinical situations.

Collaboration is not isolated to the clinical world. Research, scholarship, and clinical service delivery can be closely linked, especially in academia. Thus, practicing collaboration across disciplines and levels of training has the potential for a bidirectional transaction between scholarship and clinical practice. The paper by Germone and colleagues in this issue describes a survey of early career faculty with results that are very salient in this era of academic expectations colliding with clinical productivity demands. The unsurprising theme that junior faculty struggle to find opportunities for academic pursuits fits with the mission of this Journal: to create accessible opportunities to hone academic skills and share scholarly work. It also highlights the importance of senior faculty involving junior faculty in scholarship and the role for mentorship in supporting junior faculty career development. All the papers in this issue exemplify these values of collaboration, mentorship, and inclusion by spanning either different disciplines or levels of experience, or both.

The inaugural issue of this Journal celebrated breadth and depth of expertise in child and adolescent mental health and how to channel this expertise into action by following a strategic plan to elevate quality of and access to behavioral health services for children, adolescents, and families. This follow-up issue's theme of multidisciplinary collaboration speaks to the mechanism for channeling expertise into action: working together.

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Experiences in Academic Medicine: A Pilot Survey of Early-Career Faculty in Pediatric Mental Health

*Monique Germone, PhD; Laura Judd-Glossy, PhD; Jessica Malmberg, PhD; Julia Barnes, PhD; Lisa Costello, PhD; Marissa Schiel, MD, PhD; MaryAnn Morrow, PMHNP-BC; Scott Cypers, PhD**

Abstract

Objective. Building a successful career in academic medicine is challenging. The purpose of this study was to survey a cohort of early-career faculty regarding their perceptions of resources available to them to support their clinical, teaching, and scholarly pursuits.

Methods. An online questionnaire was emailed via SurveyMonkey to 22 early-career faculty members at the Pediatric Mental Health Institute at Children's Hospital Colorado and the University of Colorado School of Medicine. Participants were asked to indicate their perception of available departmental supports in the following domains: work-life balance, initial career expectations, mentorship, and resources for early-career faculty.

Results. Fifteen of 22 questionnaires (68%) were completed and returned. Participants included 8 psychologists (53%) and 7 medical faculty (MDs/DOs and APNs; 46%). Early-career faculty reported mixed experiences of achieving a work-life balance. Participants reported feeling the most prepared to meet the clinical expectations, yet not the scholarly expectations of their position. Most participants indicated that they had an established mentor and were unsure if the department offered supports for scholarly endeavors.

Conclusions. The results of the current survey demonstrate a continued need for supports of early-career faculty in the domains of work-life balance, initial expectations of working in academic medicine, mentorship, and resources for being successful as a faculty member.

Introduction

Careers in academic medicine can offer exciting and diverse opportunities, including direct patient care, scholarly activities, teaching, and leadership. These opportunities require substantial investments of intellectual energy, effort, and time. As a result, new faculty may find it challenging to successfully fulfill their diverse roles within academic medical centers.[1,2] Various personal and institutional factors, such as perceived failure of department leadership to foster a supportive climate (ie, inclusiveness, respect, and open communication), lack of professional development opportunities, limited recognition and support for excellence in both teaching and clinical care at an institutional level, and >50% of professional time devoted to patient care may lead to high faculty turnover.[3] Significant concerns have been raised regarding the fact that as many as 82% of new faculty in the United States seek employment in another institution within their first year of employment.[4] To prevent turnover and support new faculty, the following areas were identified in the literature as essential: support of work-life balance,[5,6] clear understanding of career expectations, [5,7-9] adequate mentorship of new faculty,[4,10-12] and knowledge of the amount and availability of institutional resources.[8,13]

Work-Life Balance

Achieving a sense of satisfaction with the relative distribution of time, energy, and resources dedicated to one's professional and personal goals is

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an especially salient issue for faculty as they navigate the formative years of their career.[5,6] Having a sense of control, achieved partially through setting clear scheduling boundaries for work and personal activities, is a key predictor of faculty satisfaction.[6] Additionally, having a sense of support from one's institution through programs and institutional policies regarding flexible workload arrangements (ie, telecommuting), schedules, and options around one's promotion clock, are important.[6]

Initial Career Expectations

Across disciplines, many studies have found that new faculty members are enthusiastic and eager to begin their new positions within academic settings.[8] However, many early-career faculty members also feel unprepared for the multiple roles and responsibilities entailed in their positions (eg, clinical work, teaching, scholarship), which can ultimately lead to job and career dissatisfaction.[7,8] Based on the literature, this lack of preparation appears to stem primarily from limited understanding of responsibilities, which may be exacerbated by a lack of relevant training and career preparation in graduate programs.[9] Specifically, limited knowledge about the expectations for promotion is the most common complaint in the literature.[5] Despite having unclear expectations for job success, many new faculty members set high expectations for their performance across all domains.[8] These self-imposed standards may be reinforced directly or indirectly by supervisors and department leaders.[8] However, new faculty members' perception of time constraints and challenges in managing competing responsibilities can negatively impact their ability to consistently meet these expectations for success.[7,8]

Mentorship

Research has demonstrated that mentoring has an important influence on a faculty member's scholarly productivity, career management, collegial networking, and career satisfaction.[4,10] Unfortunately, a relative dearth of empirical literature exists on the process of mentoring early-career faculty members in academic medicine. The traditional dyad model, where a senior faculty member mentors a junior faculty member, has consistently been shown to be the most common mentorship model, although peer mentoring has become increasingly popular.[11] The most common mentoring activity reported is regular meetings between mentors and mentees, with the frequency of meetings ranging from weekly to twice yearly.[10] While the benefits of mentorship are evident, concerns regarding the sustainability of mentorship models have been raised, given increasing clinical responsibilities, reduction of allocated time for scholarly activities, and a decline of available senior faculty to serve as mentors.[12]

Resources for Early-Career Faculty

Research has indicated that new faculty require support to establish their roles as teachers, scholars, and researchers.[8,13] Historically, new faculty have reported lower work-related satisfaction and increased work-related stress as time passes.[8] Clear guidelines and support from a faculty member's department and the senior faculty are important for junior faculty career development and satisfaction.[8,13,14] In a survey of residents, fellows, and junior and senior faculty members, Kubiak et al[14] found that in addition to mentoring, respondents requested guidelines and supports to address financial challenges such as assistance with debt management, pilot funding for scholarship and research, and academic skills acquisition (eg, teaching and presentation skills, and protected time for research and scholarly activities).

Current Aims

The current paper examines the needs of new faculty members at 1 academic medical institution by surveying early-career faculty on their approaches to and perceptions of institutional support for work-life balance, knowledge of initial career expectations, adequate mentorship, and finally, accessibility of resources. The authors were interested in discovering the extent to which new faculty (ie, academic appointment within the past 5 years) at the Pediatric Mental Health Institute (PMHI, part of Children's Hospital Colorado and the University of Colorado School of Medicine) balanced the demands of their work responsibilities and received support as early-career professionals. The faculty members at the PMHI represent a variety of disciplines including psychiatry, psychology, and advanced practice nursing, and hold primary faculty appointments within the Department of Psychiatry at the University of Colorado's School of Medicine. The PMHI now has more than 60 faculty

members (46 at the time of this survey) and provides a continuum of psychiatric services including outpatient, partial hospitalization, inpatient, consultation-liaison, and emergency services to children and adolescents.

The authors investigated whether early-career faculty felt supported in critical areas necessary for career growth, and how satisfied they were with the support they receive from the institution. This survey aimed to discover areas of strength within our institution, as well as to identify areas in which to recommend improvement.

Methods

Sample

The sample was comprised of early-career faculty within their first 5 years of initial appointment at the PMHI. At the time of the survey, this institute had a total of 46 faculty members, comprised of psychiatrists, advanced practice nurses, and psychologists. A total of 22 early-career faculty met criteria for inclusion and were invited to respond to the survey (48% of all faculty at the PMHI). Responses were received from 15 faculty members, a participation rate of 68%. Some participants did not provide answers to every question. Pairwise deletion was used to address missing data when calculating percentages pertaining to the age and racial ethnic group demographic characteristics of the sample. Demographic questions were included in the study to gather information about age, sex, race, marital status, number of children, graduate degree(s), post-degree training, current faculty title, and previous faculty appointments (Table 1). Those who completed the survey were largely female (n=12), white (n=14), and between 30 and 39 years of age (n=12). Most participants also reported that this was their first faculty appointment. In terms of degree status, 8 participants had a PhD, 3 participants had an APN degree, and 4 participants had a DO/MD. The majority of participants were ranked at the assistant professor level (n=8), while the remaining 7 participants were ranked at the instructor/senior instructor level (Table 1).

Survey Development

The authors conducted a review of the literature on issues relevant to early-career faculty. Four areas of interest were selected for focus in this survey based on their salience in the literature: (1) work-life balance, (2) initial career expectations, (3) mentorship, and (4) resources for early-career faculty. Survey questions were developed to address each of these areas (Appendix). The 34-question survey included a section on basic demographics (9 questions); a series of questions pertaining to mentorship (5 questions), departmental supports (7 questions), and work-life balance (7 questions); and perception of preparedness to meet clinical, research/scholarly, and supervisory/teaching expectations (3 questions). Question response sets included the following:

1. Forced-choice and dichotomous question types to collect demographic data and the participants' perceptions of the availability of particular programs or resources within the department (eg, "My department offers a new faculty orientation program," "Yes, No, or Not Sure").
2. Five-point Likert scales to measure the participant's attitudes and opinions regarding the selected topic (eg, "Not at all" to "Much more than I would like," or "Not at all prepared" to "Fully prepared").
3. Check all that apply questions to solicit as many responses to questions as participants perceived were applicable to them (eg, "In which ways, if any, do you set clear work-life boundaries").
4. Open-ended questions that allowed participants to offer detailed comments on their experiences.

See Appendix for a full description of the survey introduction, questions, and response sets.

Survey Administration

The survey was programmed into SurveyMonkey for self-administration. A link to the survey was emailed, along with a request for participation, to early-career faculty during the Fall of 2015. Within the email, participants were informed of the estimated length of time to complete the survey (5–10 minutes), that their responses would remain anonymous, the rationale behind the survey (to improve the supports for faculty members at PMHI), and that the results may be published in a scholarly journal. The participants were encouraged to contact the research team with questions or concerns. No incentives were offered for participation. Participants were asked to complete

the survey within 1 week and a follow-up request was made 2 days prior to the deadline to encourage a higher response rate.

Data Analysis

Data was transferred from SurveyMonkey to SPSS version 22.0 for data analysis. Descriptive analyses of responses were conducted and open-ended responses were reviewed to identify key themes. Results for each of the main areas of inquiry are described in the section that follows.

Results

Work-Life Balance

Eight of the 15 participants felt their faculty position had allowed them to achieve a work-life balance at a moderate to very-high level, while the remaining 7 participants indicated having achieved considerably less balance than they would like. In responding to ways in which they achieve work-life balance, faculty endorsed the following strategies: (1) protecting specific personal times in one's schedule (n=7), (2) checking email only at designated intervals or times (n=6), and (3) scheduling work time around childcare (n=5). When asked to outline additional strategies employed that were not explicitly listed in the survey, participants identified strategies such as completing all work on-campus, leaving cell phone/pager off when not on-call, not working on days off, and setting boundaries around work hours. For example, one faculty member reported, "Don't engage in after-hours talks or activities except on limited basis for national meetings."

Most participants reported making minimal modifications to their professional activities in order to create more work-life balance, with 8 participants responding either "not at all" or "a little" to this question. For those who endorsed having made some level of modification to their professional activities, the following strategies were endorsed: (1) engaging in fewer activities for promotion (n=7), (2) declining invitations to participate in professional activities (n=6), (3) selecting support rather than leadership roles (n=5), (4) delaying or pausing the promotion clock (n=3), and (5) reducing his/her work schedule (n=2).

Faculty overwhelmingly acknowledged that they have modified their personal life in order to engage in professional activities, with 11 of the 15 participants indicating that they had made moderate to high modifications to their personal lives. A large majority of faculty members reported that they got less sleep than was ideal (n=11); worked nights, early mornings, or weekends (n=4); and spent less time attending social events (n=12).

Initial Career Expectations

Participants reported strong readiness to assume the clinical expectations of their positions with 9 participants indicating that they felt prepared or fully prepared to meet the clinical demands of their role. Participants endorsed moderate readiness with regards to fulfilling teaching/supervisory expectations, with 7 participants feeling prepared/fully prepared. Only 2 participants felt prepared/fully prepared to accomplish research/scholarly expectations required of their positions. Participants noted feeling largely dissatisfied (n=11) with the amount of time they are allotted to accomplish all tasks required of them in their professional roles (eg, clinical, research, teaching, etc).

Mentorship

The majority of participants (n=11) had established either a formal or informal mentoring relationship with another faculty member, with 2 participants receiving mentorship from an individual at another institution. Of those with an established mentoring relationship, 11 participants reported they informally sought out their mentor. Ten of the 11 participants with an established mentorship relationship reported they meet regularly with their mentor, with the majority estimating the frequency of these meetings to be weekly or monthly. The most commonly endorsed objectives that faculty felt were important in a mentoring relationship included assistance with promotion (n=13), clarification regarding department/university faculty expectations (eg, teaching, research, clinical responsibilities; n=13), peer support (n=11), and research/scholarly support (n=11). The majority of faculty members (n=10) endorsed feeling somewhat to very satisfied with their mentor's ability to clearly delineate university expectations regarding academic promotion and support them in meeting these expectations.

Resources for Early-Career Faculty

Nine faculty members indicated they were unsure or did not believe that there was a new faculty orientation available to them. Of those who endorsed attending a new faculty orientation, only 2 participants felt they gained new knowledge regarding programs available on-campus to assist faculty with teaching or scholarly activities. When queried as to whether participants were aware of formal support/resources available to them for scholarly activities, over half (n=11) indicated they were aware of these resources, while 5 participants reported being unsure about the availability of these resources. The overwhelming majority of participants reported their department did not offer protected time or grant opportunities to support them in advancing their research/scholarly activities (n=6), or were unsure if their department offered these supports (n=8).

Discussion

The aim of the current pilot was to highlight the current perceptions of early-career faculty at an academic medical center, particularly with regard to whether they felt supported in domains critical to their career development. Despite the small sample size (n=15) and limited demographic range (predominantly white, female, ages 30–39), the responses from this survey are consistent with the literature in regard to new faculty's perceptions of work-life balance, initial career expectations, mentorship, and resources for early-career faculty. Overall, participants surveyed in this study continued to endorse the need for support in work-life balance; understanding clinical, scholarly, and teaching expectations; access to a senior-level mentor; and additional resources such as time and monetary support, especially for scholarly projects. Each critical area is discussed more in depth in the sections that follow.

Work-Life Balance

Findings from this survey suggest that self-care activities are the most common personal sacrifices that faculty make in order to fulfill work-related duties, which research points out could negatively impact one's overall sense of well-being and job satisfaction.[2] Specifically, a majority of participants indicted that they slept less in order to work during the nights, early mornings, and/or weekends. Additionally, a majority reported reducing the time they spent engaged in recreation with their families. Faculty members in this survey expressed interest in working at the institutional level to create policies to support work-life balance. In general, they recommended a need for policies that support flexible schedules, streamlined processes for using personal and professional leave time, and mentorship relationships that address work-life balance. Results of this survey support findings and recommendations within the current literature regarding the importance of institutions supporting an open discussion of work-life balance issues, both for the personal well-being of their faculty, as well as for the productivity of the institution. Readers are referred to Lee et al[15] for recommended questions that institutions may pose to faculty to facilitate such discussion, including "am I willing to make the personal sacrifices that are required to become the top person in my field–would 'well-respected' be good enough?"

Initial Career Expectations and Mentorship

Survey results demonstrated that new faculty members felt most prepared for their clinical responsibilities and least prepared for their research/scholarly expectations. It should be noted that as clinical educators, early-career faculty within the Department of Psychiatry at the University of Colorado School of Medicine have scholarship expectations that may include, but are not limited to, research activities. A shift in academic medicine has been noted in the literature with regards to research expectations.[16,17] Authors have argued that academic institutions should seek to support faculty's involvement in teaching, dissemination, and application of knowledge (ie, "scholarship"), as well as more traditional investigational research. O'Meara[16] noted that a common definition of scholarship has been difficult to agree upon and it is possible that faculty who completed this survey may have been unaware of the distinction between research and scholarship. Given that this survey specifically queried faculty about their perceived ability to accomplish research expectations and did not directly inquire about scholarly expectations, it is possible that faculty might have reported higher rates of feeling prepared to accomplish their scholarly expectations, in comparison to their research expectations, had they been asked to report on both.

Knowledge and support about the promotion process, which is typically an area of concern for most new faculty members, continues to be a target for ongoing institutional improvements. Additionally, this information highlights how a one-size-fits-all mentoring/support approach may not meet the needs of faculty who come with different levels of comfort/experience across different domains (eg, clinical, teaching, scholarship). Departments may also want to explore effective ways to balance the competing demands for new faculty, as well as the amount of time allotted to each activity, as this seems to be an area of perceived difficulty for early-career faculty.

Resources for Early-Career Faculty

On the whole, results from this section suggest a need to ensure that faculty are aware of the resources that are available to them. As over half of the participants responded that they either did not receive a new faculty orientation or were not sure if they had (n=9), this survey indicates that departments may benefit from explicitly labeling and defining new faculty orientation processes and considering the timing of orientations. Suggested components of a new faculty orientation from the literature include information regarding the distinction between research and scholarship, the day-to-day responsibilities, and also addressing ways to foster relationships between new faculty and the department in which they work.[8] While information about the promotion process is being provided, faculty may benefit from further support in how to achieve the promotion requirements. Time and money are finite resources, so educating faculty on what resources are available to support them may improve productivity and job satisfaction as only 1 participant acknowledged that these resources are available to early-career faculty.

Limitations

There were several limitations to the current study including a small sample size, all participants coming from a single department within a single institution, and exclusivity within the disciples of psychology and psychiatry. Additionally, the sample is not demographically diverse as it is comprised primarily of Caucasian women, ages 30–39. While the results of this pilot survey may not be representative of all early-career faculty, which limits the generalizability of the study, the findings from this survey are consistent with the findings from prior studies conducted on this topic.

Conclusions and Future Study

The results of the current survey demonstrate a continued need for supports of early-career faculty in the domains of work-life balance, initial expectations, mentorship, and resources. Survey responses indicated that the concerns of early-career faculty remain consistent with those noted in the literature over the past 30 years. While some faculty reported having adequate support, most reported a desire to receive additional supports in order to succeed in their careers. The faculty who were surveyed expressed an interest in assistance with work-life balance, preparedness for scholarly activities, mentorship, and feeling connected to other faculty.

Survey results depicted a preference for institutional support for maintaining a work-life balance, individualized and dynamic mentorship experiences, and explicit communication regarding resources and supports available to early-career faculty. While the experiences of early-career faculty are now well documented in the literature, future studies should continue to examine ways in which early-career faculty experiences could be improved, and how institutions can better support them in establishing themselves as professionals within academic medicine.

Table 1. Demographic Characteristics of Commentary Sample (n=15)

Note: Pairwise deletion was used to address missing data when calculating percentages.

Characteristic	Number	Percent
Age		
30-39	12	85.7
40-49	1	7.1
50-59	1	7.1
Missing*	1	--
Gender		
Female	12	80
Male	3	20
Degree		
MD/DO	4	26.6
APN	3	20
PhD	8	53.3
Married/Partnered		
Yes	14	93.3
No	1	6.7
Children		
Yes	10	66.7
No	5	33.3
Racial Ethnic Group		
White	14	100
Missing*	1	--
Prior Faculty Positions		
Yes	3	20
No	12	80
Years with Current Dept		
<1 year	4	26.7
1-2 years	5	33.3
2-3 years	4	26.7
3-4 years	2	13.3
Faculty Title		
Instructor	2	13.3
Senior Instructor	5	33.3
Assistant Professor	8	53.3
Years of Post-Degree Training		
1 Year	7	46.7
2 years	3	20
5+ years	5	33.3
Training from Current Dept		
Yes	7	46.7
No	8	53.3

Appendix. Early-Career Faculty Survey

Introduction

We appreciate your time and support of our project, which is examining the experience of early career faculty. Please note that your responses will remain anonymous and the questions have been designed to help protect your anonymity.

If the following questions ask for your opinions regarding your "department," this references the Pediatric Mental Health Institute (previously known as the Department of Psychiatry & Behavioral Sciences) at Children's Hospital Colorado.

Questions with an asterisk (*) identifies a question that requires a response.

Questions

Mentorship

Several studies have indicated that development of a mentor relationship when new faculty members are hired impacts the overall success of those members' assimilation into the culture of the institution, their job satisfaction, and their ability to smoothly navigate their career path. Please tell us about your mentoring experience regarding our present position at PMHI.

1. Have you established a mentor relationship with another faculty member? (Select all that apply)*
    a. No, I have not established a mentor relationship.
    b. Yes, I was formally assigned a mentor from this institution.
    c. Yes, I informally sought out a mentor from this institution.
    d. Yes, I informally sought out a mentor from another institution.
    e. Other (please specify)
2. How do you access mentorship from your mentor?*
    a. Not applicable. Do not have a mentor.
    b. Informal pop-in meetings
    c. Communicate primarily through email
    d. Do not meet/communicate
    e. Regularly scheduled meetings (please specify frequency)
3. What objectives do you feel are important in a mentor relationship? (Select all that apply)*
    a. Promote faculty development/assist with promotion process/tenure process
    b. Peer support
    c. Liaison with others in the department/regionally/nationally
    d. Resource concerning university/department expectations for faculty (eg, teaching, research, clinical responsibilities)
    e. Formal support for research and scholarly work
    f. Not applicable. Do not feel a mentor relationship is important
    g. Other (please specify)
4. How helpful has your mentor been in assisting you with socializing and developing collegial relationships with your colleagues in the department/regionally/nationally?*
    a. Not at all helpful
    b. (intermediate choice)
    c. Somewhat helpful
    d. (intermediate choice)
    e. Very helpful

5. How satisfied are you with your mentor's ability to clearly delineate department expectations regarding research, teaching, and clinical responsibilities?*
    a. Very unsatisfied
    b. (intermediate choice)
    c. Somewhat satisfied
    d. (intermediate choice)
    e. Very satisfied

Developmental Supports

Below are some ways a department can support their new faculty. Please think of the supports provided by PMHI/CHCO Department of Psychiatry & Psychology when responding to the following questions.

6. My department (PMHI) offers a new faculty orientation program.*
    a. Yes
    b. No
    c. Not sure

7. The new faculty orientation program at PMHI helped me to build relationships with other faculty members.*
    a. Yes
    b. No
    c. Not sure
    d. Not Applicable. Did not have a faculty orientation program.

8. The new faculty orientation program at PMHI supplied me with information about teaching, research, and campus programs.*
    a. Yes
    b. No
    c. Not Sure
    d. Not Applicable. Did not have a faculty orientation program.

9. My department has a formal support program for research and scholarly work.*
    a. Yes
    b. No
    c. Not sure

10. My department offers released time and/or grant-in-aid opportunities to provide resources to advance and strengthen my research record.*
    a. Yes
    b. No
    c. Not Sure

11. How satisfied are you with the time you have been provided to complete required tasks (clinical, teaching, supervising, research)?*
    a. Not at all satisfied
    b. (intermediate choice)
    c. Somewhat satisfied
    d. (intermediate choice)
    e. Very satisfied

12. Have you been provided guidance about the promotion/tenure process?*
    a. Yes
    b. No
    c. Not Sure

13. How satisfied are you with the level of support/guidance you have received in starting to accomplish tenure requirements (teaching, research, committees)?*
    a. Not at all satisfied
    b. (intermediate choice)
    c. Somewhat satisfied
    d. (intermediate choice)
    e. Very satisfied

Work-Life Balance

For the purposes of this survey we are defining work-life balance as a sense of clear boundaries in time and attention focused on professional versus personal activities.

14. To what extent has your faculty position allowed you to achieve work-life balance?*
    a. Much less than I would like
    b. (intermediate choice)
    c. Somewhat
    d. (intermediate choice)
    e. Achieved a very high level

15. In which ways, if any, do you set clear work-life boundaries (check all that apply):*
    a. Have not set boundaries
    b. Check email only at designated intervals or times
    c. Protect specific personal times in your schedule
    d. Schedule non-negotiable writing time
    e. Schedule work time around child care
    f. Other (please specify)

16. To what extent have you modified your professional activities to create more balance in your personal life?*
    a. Not at all
    b. (intermediate choice)
    c. Somewhat
    d. (intermediate choice)
    e. Much more than I would like

17. In which ways, if any, have you modified your professional activities to create more balance in your personal life (check all that apply):*
    a. Have not made modifications
    b. Reduced work schedule
    c. Selected support rather than leadership roles
    d. Delayed or paused the tenure clock
    e. Declined invitations to participate in professional activities
    f. Chose a mentor based on impressions of their own work-life balance
    g. Engaged in fewer activities for promotion (eg, teaching, clinical activity, research, service, scholarship). Please specify.

18. To what extent have you modified your personal life to engage in professional activities?*
    a. Not at all
    b. (intermediate choice)
    c. Somewhat
    d. (intermediate choice)
    e. Much more than I would like

19. In which ways, if any, have you modified your personal life to engage in professional activities (check all that apply):*
    a. Have not made modifications
    b. Delayed having, spacing when, or choosing to not have children
    c. Get less sleep than is ideal
    d. Worked nights, early morning and/or weekends
    e. Spent reduced time on nights and weekends attending personal/family activities
    f. Did not attend certain personal/family activities

20. To what extent do you perceive that there are policies in place to support adequate work-life balance (eg, availability of and ability to use leave time; availability for coverage)?*
    a. Not at all
    b. (intermediate choice)
    c. Somewhat
    d. (intermediate choice)
    e. Very much

21. What would make it easier to have more work-life balance as an early career faculty (eg, working remotely, flexibility in schedule, research partnerships)?*

Expectations

22. Many academic positions include expectations for success within clinical, research, and supervisory domains. How would you describe your preparation to meet the clinical expectations of your role?*
    a. Not at all prepared
    b. (intermediate choice)
    c. Somewhat prepared
    d. (intermediate choice)
    e. Fully prepared

23. How would you describe your preparation to meet research expectations?*
    a. Not at all prepared
    b. (intermediate choice)
    c. Somewhat prepared
    d. (intermediate choice)
    e. Fully prepared

24. How would you describe your preparation to meet the supervisory expectations?*
    a. Not at all prepared
    b. (intermediate choice)
    c. Somewhat prepared
    d. (intermediate choice)
    e. Fully prepared

Demographics

Thank you for taking the time to complete this survey. We appreciate your responses. Below are questions regarding demographic variables. You may answer as many, or as few, as you like. Please note that your responses help us to better understand our data and ultimately in helping our department.

25. Age
    a. 21-29
    b. 30-39
    c. 40-49
    d. 50-59
    e. 60-69

26. Gender
    a. Male
    b. Female
27. Race
    a. White
    b. Black or African American
    c. American Indian or Alaska Native
    d. Asian
    e. Native Hawaiian or Other Pacific Islander
28. How many years have you been a faculty member at PMHI/CHCO Department of Psychiatry & Behavioral Sciences? Please do not include the time you were in formal training with this department.
    a. <1 year
    b. 1-2 years
    c. 2-3 years
    d. 3-4 years
    e. 4-5 years
29. Faculty Title
    a. Instructor
    b. Senior Instructor
    c. Assistant Professor
    d. Associate Professor
    e. Full Professor
    f. Other (please specify)
30. Degree
    a. MD
    b. APN
    c. PhD
    d. PsyD
    e. Other (please specify)
31. Years of Post-Degree Training
    a. 1 year
    b. 2 years
    c. 3 years
    d. 4 years
    e. 5+ years
32. Did you receive any portion of your training (pre-degree, post-degree, or both) at PMHI/CHCO Department of Psychiatry & Behavioral Sciences?
    a. Yes
    b. No
33. Married/Partnered
    a. Yes
    b. No
34. Children
    a. Yes
    b. No

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Adherence in Adolescent Transplant Patients: Exploring Multidisciplinary Provider Perspectives

*Sarah L. Kelly, PsyD; Elizabeth Steinberg, PhD; Cindy L. Buchanan, PhD**

Abstract

Introduction. Solid organ transplantation is viewed as a chronic illness that requires strict adherence to a complex post-transplant medical regimen. Adolescent transplant recipients are most at risk for serious and potentially fatal outcomes as a result of poor medication adherence. There are several psychosocial and behavioral factors that contribute to nonadherence, but few well-studied psychological interventions exist. Provider perspectives are crucial to understanding the unique needs of this population to inform effective and acceptable interventions.

Methods. An 11-item quantitative and qualitative survey was developed and completed by 34 transplant providers among the pediatric heart, liver, and kidney teams at a children's hospital as part of a quality improvement project.

Results. Providers reported that in their experience most adolescents struggle with adherence (67%) and indicated that they dedicate a great deal of time, emotional energy, and clinical resources to address nonadherence—given its serious consequences. Providers identified factors they believe contribute to adherence in their adolescent patients, such as forgetting/poor planning, emotional and behavioral problems, family conflict, and poor parental monitoring. They offered suggestions for improved adherence assessment as well as behavioral interventions aimed at improving adherence, such as peer support groups, perhaps delivered via videoconference, to make them accessible to this geographically-dispersed population.

Discussion. Pediatric transplant providers recognize the need for identification of nonadherence, standardized assessment of associated risk factors for nonadherence, and innovative treatment options for this vulnerable population. Results of this quality improvement project informed changes in how Transplant Psychology collaborates with the solid organ transplant teams to assess and treat adherence in the pediatric transplant population at our children's hospital.

Introduction

Solid organ transplantation is a life-saving treatment option for many acute and chronic end-stage diseases with dramatically improved survival rates and outcomes over the past few decades. Though a transplant increases longevity and improves quality of life, it is also best conceptualized as a chronic illness requiring strict adherence to a complex post-transplant medical regimen.[1] Postoperatively, it requires twice-daily life-long immunosuppressant medications, frequent laboratory blood draws, close medical follow-up, and unpredictable hospitalizations for infection or rejection episodes, among other medical cares. Medical adherence has been defined as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."[2] Adherence is a complex health-related task that is essential for long-term graft survival in pediatric solid organ transplant recipients. Definitions of graft

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rejection, survival, and loss or failure vary based on organ type.[3] For the purposes of this article, acute graft rejection is typically characterized by rapid, progressive deterioration of graft function associated with specific pathological changes that may be reversible if treated promptly. Chronic rejection refers to the gradual decrease in function of the graft. Graft survival refers to the success of the transplanted organ and contrasts the terms "graft loss" or "graft failure," which are defined as irreversible loss of function of the organ. In particular, nonadherence with immunosuppressant medications is associated with serious and potentially fatal consequences, including medical complications, graft rejection and failure, post-transplant mortality, and increased health care utilization and costs.[1,4]

Assessment of Adherence

Nonadherence can range in severity, and medical consequences are dependent on disease process and health status. The term "nonadherence" is used throughout this article to capture the spectrum of adherence behaviors, from occasional missed doses of medication to significant lack of adherence to medications or other medical care, especially since, in transplant, even minor lapses in adherence can have negative health consequences. Additionally, adherence, though often conceptualized as a stable characteristic, can change over time, and typically worsens after transplant.[1,5] Adolescence is a developemental phase marked by significant gains in cognitive and socioemotional development during which many healthy and risky health behaviors emerge and consolidate. Thus, adherence behaviors and health habits during adolescence establish a trajectory that has implications for health as an adult.[6] Research has consistently identified adolescents and young adults as the most at-risk for nonadherence to medication regimens. Nonadherence in pediatric solid organ transplant patients is estimated as high as 50%-70%, and contributes to more graft loss than uncontrolled rejection in adherent patients.[7-11] The medical impact of nonadherence is staggering for transplant recipients, and nonadherence is also related to poor psychological and social outcomes.[12] For example, nonadherence in pediatric transplant recipients has been associated with decreased health-related quality of life, social and school activities, family cohesion, increased emotional and behavioral problems, and parental distress.[8]

Given the severity of potential consequences of nonadherence and the magnitude of this problem in the adolescent population, pediatric transplant researchers have worked to identify the individual, family, and environmental factors that contribute to nonadherence. The causes of nonadherence are multifactorial and exacerbate the burden of the chronic illness itself. Risk and protective factors are delineated within the World Health Organization's 5 interrelated categories (see Figure 1): Patient-related factors, Socio/economic factors, Condition-related factors, Therapy-related factors, and Health system/HCT-factors.[2,7]

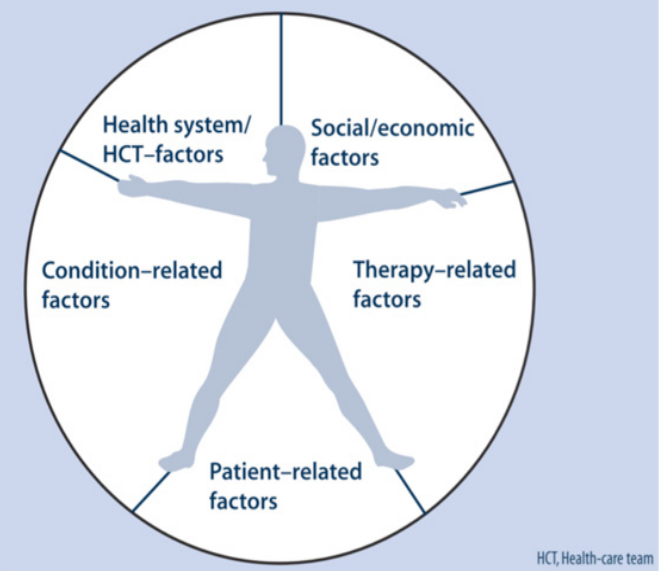

Figure 1. The 5 dimensions of adherence[2]

Patient-related factors include medication knowledge; understanding of disease; forgetfulness; cognitive abilities; self-esteem; emotional, behavioral, social, and school functioning; and coping.[13] Additionally, patient-related factors associated with the critical and normative developmental tasks of adolescence, including establishing autonomy and self-identity, can contribute to adherence or nonadherence, such as perceived injustice, sense of immortality, peer acceptance, and body image.[14-15] For youth, patient-related factors also include family variables, such as caregiver supervision (eg, lack of monitoring of medication-taking versus parental anxiety and overprotection), family environment, communication, parental mental health, and social support.[7,8] Socioeconomic-related factors include socioeconomic status, health literacy, stability of housing, health care insurance, and medication cost. Factors related to condition, therapy, and health care include severity and duration of illness,

treatment regimen complexity, side effects, trust and communication with health care team, amount of health information and follow-up, health beliefs, and access to care; these factors are especially important to consider given the common bias in prior research to focus more attention on patient or familial characteristics as contributors to nonadherence with less investigation into health care system contributors to nonadherence.[7]

Other transplant research has investigated adolescent and parent reports of barriers to medication adherence, indicating the domains of disease frustration/adolescent issues, regimen adaptation/cognitive issues, and ingestion issues (eg, inability to swallow medications, bad tasting medicine, etc).[16] Higher selection of barriers was related to nonadherence, and barriers are stable over time and unlikely to decrease without intervention.[17-21] Nonadherence is more likely when adolescents are fully responsible for medication administration (rather than parents), and adherence is significantly worse with morning doses than with evening doses.[20] Adolescents tend to report more emotional and social barriers to adherence, while parents typically identified more challenges with regimen adaptation and cognitive barriers.[21] Furthermore, common patterns of nonadherence in transplant recipients fall into 3 distinct profiles: (1) accidental non-compliers, or those who struggle with organization and forgetfullness; (2) invulnerable non-compliers, or those who do not believe they need to take their medication; and (3) decisive non-compliers, or those who independently decide not to adhere.[22]

Interventions for Nonadherence

Interventions for children and adolescents with chronic illness typically address adherence with behavioral, educational, and organizational strategies, with many treatments combining 2 or more of these approaches.[23] A meta-analysis by Graves and colleagues[23] found that the effect size across all of the adherence outcomes for group design intervention studies was in the medium range, and single-subject design studies' effect size was in the large range, demonstrating that adherence interventions are effective for increasing adherence. Furthermore, treatments must be attentive to developmental aspects of care, health beliefs, and cultural considerations.[15,24-25] However, there remains a paucity of research into the creation and systematic investigation of culturally- and developmentally-sensitive behavioral interventions to improve adherence specifically in pediatric transplant recipients.

New interventions for youth with chronic illness have focused on utilizing technology, such as mobile applications, videoconferencing, and Internet-based support groups, to both increase the possible intervention participants and to appeal to adolescents' interest in technology.[26] Utilizing technology in practice can improve patient outcomes, increase access to care, and reduce the burden of illness and treatment; teens are a key audience due to their comfort and familiarity with technology.[27] Youth often set phone alarms for medication administration, and they have easy access to phone and tablet applications, including software to encourage medication monitoring and electronic reminders. Indeed, electronic reminders have demonstrated effectiveness for short-term adherence improvements, though long-term effects have not yet been determined.[28] There is also widespread patient acceptance for telehealth, but there are challenges in providing these services, especially home-based telehealth, including reimbursement. Nonetheless, progressive changes in the digital health care landscape seem promising for further advances in telehealth reimbursement and implementation. However, to date, there are no telehealth adherence interventions focused specifically on adolescent solid organ transplant recipients.

Current Standard of Care

When adolescent solid organ transplant recipients are identified as nonadherent, or at risk for nonadherence, there are several steps that medical teams can take, including increasing the frequency of lab blood draws, increasing the frequency of outpatient medical visits, or even admitting the patient to the inpatient medical floor for medication administration and close monitoring.[19] Transplant-specific education, for both parents and teens, is an essential ingredient of effective interventions and should involve clear communication, shared decision-making, specific goals, and written information.[19,29] However, education and knowledge are not sufficient to spur lasting results.[7,23,30] There are other tactics medical staff can try, including attending to the patient-provider relationship, simplifying the medical regimen if possible, ad-

dressing problematic side effects, praising adolescents for even small successes, and allowing plenty of time for questions.[13,31-32] If medical teams are concerned about parental functioning or if social, financial, legal, or logistical barriers are identified, social work often becomes more involved.[33] In addition, providers make a referral to psychology for inpatient or outpatient health and behavior interventions to provide individual or family support and skills training in strategies that will improve adherence.[34] If clinically-concerning emotional symptoms are identified, a formal diagnostic evaluation is conducted to offer a full assessment and recommendations for clinical management that may include psychology and/or psychiatry services. However, pediatric transplant centers vary significantly in their procedures and capacity to provide optimal level of care for many adolescents at-risk for nonadherence,[7] and more research is needed to advance the assessment and treatment of nonadherence in adolescent transplant recipients.

Provider Perspectives

Provider trust and relationships are also important aspects of adherence for teens with chronic illness.[31] Health care providers serve a critical role in identifying adherence problems, implementing immediate strategies to help patients, and referring families for more intensive support. However, there is a paucity of literature about provider perspectives on adherence in pediatric transplant populations. One study of pediatric renal transplant recipients assessed physician ratings of reasons for nonadherence and found that the primary reasons asserted by physicians were family-related variables—lack of parental supervision and parent-child conflict.[11] Provider perspectives are invaluable given their long-term relationships with their patients, and their input is key to target interventions in a successful and sustainable manner. Research demonstrates that patient trust in medical team providers, as well as satisfaction with psychosocial aspects of care, are related to adherence,[13] and adolescent satisfaction and trust with health care providers is related to provider honesty, trust, respectfulness, and perceived competency.[35] While there is an established standard of care for adolescent transplant recipients with adherence problems, there is a lack of research on the effectiveness of adherence interventions focused on organ transplant recipients, and even less research specifically focused on adolescents in this population, despite their vulnerability.[12, 31,35]

The objective of the current quality improvement project was to assess multidisciplinary transplant provider perspectives of adolescent nonadherence for a population of kidney, liver, and heart transplant recipients at a large children's hospital and pediatric transplant center. Another objective of the survey was to inform future psychology and multidisciplinary programming at this transplant center, as there is a need for additional behavioral health interventions for adolescents with transplants.[18]

Methods

Setting

Our pediatric transplant center offers kidney, liver, and heart pre-transplant evaluation; single-organ transplantation; and post-transplant follow-up care. The center was established more than 25 years ago and has performed over 400 heart, 200 liver, and 250 kidney pediatric transplants; in 2015, 14 heart, 22 kidney, and 16 liver transplants were performed. The center utilizes a multidisciplinary team approach with a variety of medical, psychosocial, and support service staff involved in the care for the over 500 patients receiving ongoing transplant care at the hospital. Transplant Psychology is integrated into the multidisciplinary transplant teams and is a standard component of transplant inpatient and outpatient care. Transplant psychology is available to identify, assess, and treat adolescent nonadherence. Additionally, Transplant Psychology and social work facilitate a monthly parent support group in an effort to better address the psychosocial needs of parents.

Procedures

We developed an 11-item mixed quantitative and qualitative survey based on adherence literature and clinical experience (see Appendix). The survey was distributed by email to 61 clinical providers working with heart, liver, and kidney transplant teams to complete anonymously. The survey included the following sections: (1) provider knowledge and perspectives on cause(s) of adherence difficulties in this population, (2) frequency of provider assessment of adherence, (3) provider estimates on how many patients struggle with adherence, (4) provider attitudes and experiences with nonadherence in adolescent patients, (5) pro-

vider interventions to address poor adherence during routine patient contacts, and (6) provider beliefs about what would be helpful or necessary to improve adherence in our adolescent solid organ transplant recipients. This quality improvement project was approved by the hospital's Organizational Research Risk and Quality Improvement Review Panel.

Analyses

Descriptive statistics and frequencies were calculated for quantitative data. Qualitative data were examined for themes and subthemes, practical and programmatic suggestions, and exemplar quotes to provide rich description of provider perspectives through the application of grounded theory and open coding.[36]

Results

The 34 respondents (55.7% response rate) of this survey included 10 transplant physicians, 7 transplant coordinators (nurses or nurse practitioners), 3 transplant surgeons, 2 other physicians, 2 residents/fellows, 3 nurses, 1 dietician, 4 social workers, 1 child life specialist, and 1 pharmacist. Given that providers in the kidney and liver transplant programs occasionally overlap, 11 work with the heart transplant program, 17 with the liver transplant program, and 16 with the kidney transplant program.

Perceived Adherence

Providers reported on the percentage of adolescent transplant recipients they believe have difficulties with medical adherence (see Figure 2), with a mean estimate of 67%.

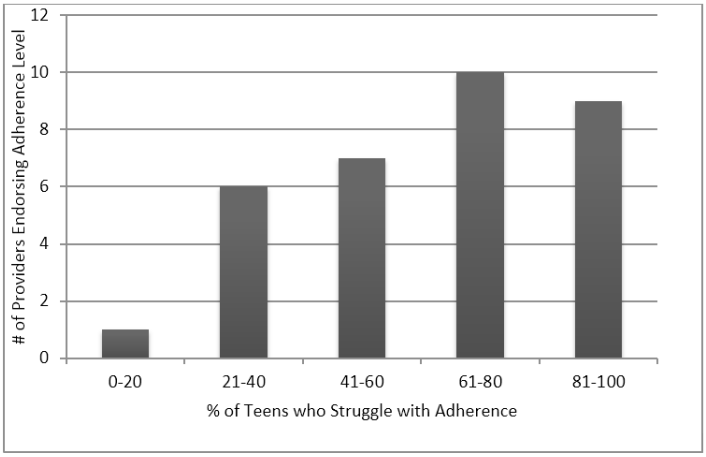

Figure 2. Percentage of adolescent transplant recipients providers believe struggle with adherence

Providers commonly ask adolescents about medication adherence, with 71% indicating that they inquire about adherence very frequently, 24% frequently, and 6% occasionally. When asked about how often they think adolescents are being truthful about their adherence, 32% indicated frequently, 62% occasionally, and 6% rarely.

Providers identified numerous factors they believe contribute to nonadherence (see Figure 3). The number of factors indicated by providers ranged from 8 to 17 and over 80% of providers selected the top 5 factors: (1) forgetting/poor planning, (2) emotional problems, (3) behavioral problems, (4) family conflict, and (5) poor monitoring (of medication taking) by parents. Additional reasons provided in open-ended responses included lack of parental emotional attention/family environment, lack of social life, desire for attention from hospital staff, health literacy, and "some [patients] just don't seem to care."

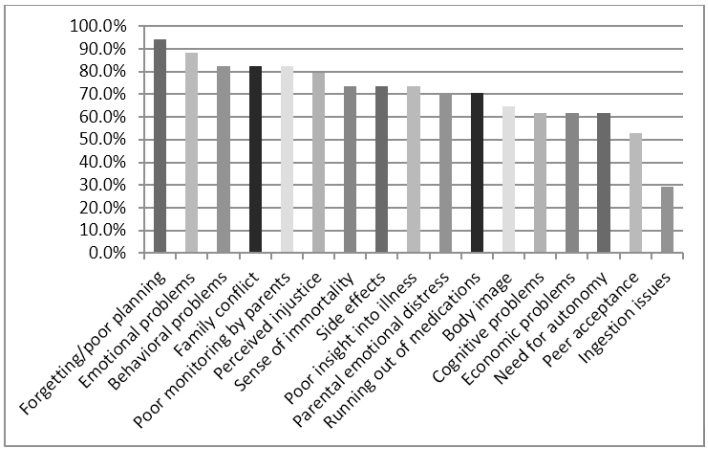

Figure 3. Factors providers believe contribute to nonadherence

Addressing Adherence in Clinical Practice

Providers reported addressing adherence in 5%-100% of their interactions with their adolescent patients, with a mean of 25% of interactions (see Table 1). We were unable to identify any differences in the percentage of interactions addressing adherence by provider type or organ type.

Almost all of the respondents agreed (85%) or strongly agreed (12%) that it is their responsibility to discuss adherence with adolescents. The following quotation highlights the importance of a team approach to addressing adherence:

> It's a team effort. Initially, the more medically trained staff (MDs and RNs) should speak

> to the patient and family regarding medications, what they do to help their body, and how important it is to take them. Then, other staff (Child Life, Psychology, Social Work, etc) can get involved to build rapport and provide continued support around why it's difficult to adhere, problem-solving, therapeutic interventions, etc.

In response to an open-ended prompt to describe their frustrations with adolescent nonadherence, providers identified the risk of rejection, death, or preventable loss of the donor organ and need for re-transplant; lack of parental ability to appropriately supervise adherence and provide support; lack of adolescent insight into the risks; lack of honesty; and difficulties educating adolescents and their families and motivating them towards better adherence by "getting them to see the bigger picture." Providers focused on the severity of consequences to nonadherence, and used strong words to express these consequences, such as "waste of a precious resource (the organ)," "rejection of the precious organ," "knowing this could be a death sentence," and "they are wasting a precious gift!" Furthermore, the consequences of nonadherence were noted to affect not just the teen's health, but their emotional well-being and the people around them, including their family members and the staff.

Improving Adherence

Further open-ended responses highlighted that 2 providers acknowedged frustrations in the way their teams handle adherence, indicating that there are steps the staff could take to improve adherence of patients. One participant stated, "I think we fail to support them enough and make ourselves available." Another participant noted the following:

> For us not to learn from teens who don't succeed and then be able to apply those lessons to the next person. I think we tend to put everyone in the same 'pot' and say they're just all teens. I believe there are some specifics that can be looked at.

Providers offered several suggestions to improve adherence in their open-ended responses, including a spectrum of pre- and post-transplant interventions and "an organized team approach." They outlined ideas for education on disease and encouraging increased autonomy, parent involvement, and support from transplant team members. They recommended ongoing monitoring and individualized treatment tailored for the specific reason(s) for nonadherence and cognitive development, and they highlighted the importance of providing emotional support and offering mental health treatment. Other suggestions included behavioral interventions, such as schedules and routines, reinforcement and rewards, motivational interviewing, and problem solving.

Two important themes emerged from providers' suggestions regarding how to improve adherence. First, the providers emphasized the critical role of peer support. For example, they suggested peer support could be facilitated by offering a teen support group, utilizing peer role models, or having a teen speaker discuss how he or she required a re-transplant due to nonadherence. This was evidenced by ideas such as:

- "Peer support groups with other transplant survivors"
- "Teen support group counseling"
- "Support groups, help seeing that this chronic illness is part of them but shouldn't stop them from doing everything they want to (including being normal)"
- "Learning from other teens who have failed transplants from nonaderence"

Second, the novel use of technology (phones, computers, apps, social media) was identified as a potential medium for interventions, with suggestions such as:

- "Easy reminders (cell phone alarms, texts)"
- "Contemporary methods to remind them—text or social media based reminder system"
- "Maybe something tech related that would be easy to use and something that could easily integrate on their phones/computers to assist them to remember"
- "Monitoring devices that tell us how often they open their pill bottle"

Discussion

Assessment of Adherence

The finding that providers believe most of their adolescent patients struggle with adherence is consistent with the literature and is also reassuring given previous findings that providers tend to overestimate the levels of adherence of their patients.[37] Providers reported they frequently ask about adherence, though they remain skeptical about adolescents' honesty regarding adherence. This skepticism is warranted given research that adolescents tend to over-report their adherence.[10] Additionally, responses to open-ended questions clearly indicated that nonadherence elicits strong feelings in providers of transplant recipients. Provider perspectives of adolescent adherence and the significant amount of time and resources dedicated to addressing adherence were consistent across provider type and the 3 organ transplant teams, suggesting that adherence is a critically important issue regardless of provider or organ type.

Providers highlighted the importance of ongoing monitoring of adherence, which aligns with research indicating that pre- and post-transplant screening, monitoring, prevention, and early intervention set the stage for success.[15] Adherence measures such as the Adolescent and Parent Medication Barriers Scales,[16] the Medical Adherence Measure,[38] and the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS)[39] can be useful in eliciting accurate and truthful reports of adherence, particularly in conjunction with immunosuppressive laboratory assays and collateral information from the medical team. Literature suggests that collecting data from multiple sources of information is more sensitive to detecting nonadherence than 1 method alone and provides comparable estimates to electronic monitoring, such as the Medication Event Monitoring System that tracks each time a pill bottle is opened.[40]

Providers indicated that behavioral and emotional factors, family factors, and relationship with transplant team are associated with adherence in their patients, which is consistent with prior literature and highlights targets for intervention.[7] Increased attention to patient-related factors that may contribute to nonadherence in this population should be incorporated into standardized inquiries about adherence. Specific questions about the following would be helpful to include in a clinical visit: (1) individual factors (eg, forgetfulness, emotional or behavioral problems, development, and lack of insight), (2) family factors (eg, conflict or lack of supervision), and (3) social and peer factors. Socio-economic factors (eg, health literacy) and health-care factors (eg, need for more support from team, need for increased availability of providers to address adherence) were also identified and could be easily incorporated into assessment during a post-transplant follow-up clinic visit. A thorough assessment of nonadherence is the first step in defining the problem before implementing interventions.

Interventions for Nonadherence

Improving adherence is a team effort, but it can be frustrating for providers, especially given the severity of the consequences of nonadherence. Provider open-ended responses emphasized the emotional impact adolescent nonadherence has on providers. Indeed, the responses to this survey indicate that providers remain dedicated not only to the well-being of the patient and family, but also to the ethics of protecting the donated organ in the context of donor organ shortages.

Providers offered thoughtful suggestions for addressing these contributing factors in ways that can be tailored to the needs and preferences of each patient, including education, mental health treatment, and individual and group social support for parents and adolescents. Their suggestions align with the research supporting multicomponent interventions designed to address the unique predictors of and barriers to adherence in adolescents.[23, 30-31] Individual behavioral interventions for medication adherence utilize self-monitoring, behavioral modification, and problem-solving to address barriers to adherence, such as peer acceptance concerns. Evidence-based treatments (eg, Cognitive-Behavioral Therapy, Interpersonal Therapy, Acceptance and Commitment Therapy, Dialectical Behavioral Therapy) address mental health problems, such as Major Depressive Disorder, which can negatively impact adherence.

Providers highlighted the importance of family supervision of care and monitoring of adolescent medication-taking (eg, verifying that a medicine was taken, ensuring that a pill-box is stored in a convenient location); these strategies should be encouraged to improve adherence.[41] Additionally, family inter-

ventions help parents implement positive reinforcement for adherence behaviors, decrease problematic interactions that may serve as barriers, and increase structure and routine around medication-taking.[41] In pediatric transplant, as like other chronic medical conditions, family members may benefit from referrals for their own mental health treatment or from peer/group support, especially if they have inadequate social support.[42]

Advancing the Standard of Care

Results of the provider survey and existing literature emphasizes that adherence must be assessed in the context of the various systems that impact adherence. Building on the results of this survey, our transplant psychology team has worked to enhance adherence services available to the children and families treated at this children's hospital. To improve identification and assessment of adherence, we have implemented routine screening, including utilization of the Parent and Adolescent Medication Barriers Scale.[16] For example, in the Kidney Center, we have begun meeting with the multidisciplinary team prior to each clinic to address psychosocial concerns and monitor the standard deviation of the last 5 immunosuppressant levels to target patients that would benefit from psychology involvement at clinic visits.

Though adolescent group treatment has not historically been offered, not only have the providers identified teen peer support as a need, but the families have also identified this need in their clinic visits. One significant challenge to hosting a teen group is the significant distance that most of our patients must travel to the hospital, with the majority of our families residing greater than 100 miles away. Many patients complete their labs and follow-up care with their primary care physicians. However, individual, family, or group behavioral health services, especially that are sensitive to unique transplant issues, are scarce outside metro areas. Providers emphasized the utility of technological interventions with adolescent transplant recipients, which could utilize individual and group telehealth treatment. Currently, Transplant Psychology is implementing and investigating the acceptability, feasibility, and effectiveness of a 5-session adolescent adherence group intervention delivered via telehealth. Technology and telehealth could expand individual and group services with patients, parents, or siblings to offer the full spectrum of family-centered services and increase access to evidence-based care at this pediatric transplant center.

Limitations and Future Directions

This project has methodological limitations, including a small sample size, participation of transplant teams at a single hospital, and lack of a rigorous survey design process or pilot test. To move from quality improvement to research that generates generalizable knowledge, future studies should survey teams at multiple hospitals and conduct a more formal pilot testing of the survey. This would increase the survey sample size and diversity, which would allow researchers to explore more nuanced relationships, such as differences between providers or organ type across different transplant teams with various levels of exposure to behavioral health assessment and intervention. While this project included providers of heart, liver, and kidney transplant teams, future survey projects could include information from providers of other solid organ or tissue transplant programs, such as lung, multivisceral transplant, and other multi-organ transplants. Provider perspectives could also be compared to patient and caregiver perspectives to enhance our understanding of adherence across contexts as well as to clinical data such as immunosuppressant laboratory values, and clinical outcomes. While many patient- and family-related factors of adherence were identified in this project as avenues for further intervention, few of the other World Health Organization's risk and protective factors (Figure 1) were identified including a lack of mention of socio-economic, condition-related, therapy-related, and health-care factors. Patients and families may be better suited than providers to identify such factors. Despite these limitations, this quality improvement project provides important guideposts for improving the transplant psychology service and multidisciplinary psychosocial care at our hospital and ultimately the outcomes of the adolescent patients we serve.

Table 1. Time spent discussing adherence and provider perspectives on adherence by provider and organ type

	Provider Type		Organ Type	
	Transplant Coordinators & Physicians	Other Team Members	Abdominal	Heart
Mean % of Clinic Visits Spent Discussing Adherence	24	27	27	20
Mean % of Teens Providers Think Struggle w/Adherence	69	64	67	66

Appendix

Adolescent Transplant Adherence: Provider Survey

Thank you for taking the time to complete this brief survey. We hope to learn more about your perspectives on adherence in adolescent transplant patients. Please keep in mind the adolescent transplant patients that you provide clinical care to when you answer the following questions:

1. Provider Type (check one)
    a. Transplant Coordinator
    b. MD–Surgeon
    c. MD–Transplant Attending
    d. MD–Other Transplant Team Physician
    e. MD–Resident or Fellow
    f. Advanced Practice Provider (non-transplant coordinator)
    g. RN (non-transplant coordinator)
    h. Social Worker
    i. Pharmacist
    j. Dietitian
    k. Psychology
    l. Child Life Specialist
    m. Other:
2. Transplant Population that you work with (check all that apply)
    a. Liver
    b. Kidney
    c. Heart

3. What factors do you think contribute to nonadherence in adolescent transplant patients? (check all that apply)
    a. Forgetting/poor planning
    b. Emotional problems
    c. Behavioral problems
    d. Cognitive problems
    e. Economic problems
    f. Parental emotional distress
    g. Family conflict
    h. Perceived injustice or desire to be normal
    i. Sense of immortality
    j. Peer acceptance
    k. Body image
    l. Side Effects
    m. Ingestion Issues (eg, Inability to swallow medications, bad taste)
    n. Need for autonomy
    o. Poor monitoring by parents
    p. Running out of medications
    q. Other:
4. How frequently do you ask about medication adherence in your interactions with teenage patients?
    a. Very Frequently
    b. Frequently
    c. Occasionally
    d. Rarely
    e. Very Rarely
    f. Never
5. What percentage of your clinic visits or interactions with teens do you spend focused on discussing adherence? (fill in the number) ___%
6. What percentage of adolescent transplant recipients struggle with adherence? ___%
7. How often to you think your adolescent patients are being truthful about their adherence?
    a. Very Frequently
    b. Frequently
    c. Occasionally
    d. Rarely
    e. Very Rarely
    f. Never
8. I believe it is my responsibility to discuss adherence with my adolescent patients.
    a. Strongly Agree
    b. Agree
    c. Undecided
    d. Disagree
    e. Strongly Disagree
9. Whose responsibility is it on the team to discuss adherence?
10. What are your biggest frustrations with nonadherent teens?
11. What kind of help do you think teens need to improve adherence?

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Regression, Depression, and Psychosis in a Young Adult Female with Down Syndrome: A Case Report

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Introduction

There have been previous reports in the literature of adolescents and young adults with Down syndrome (DS) experiencing significant behavioral and cognitive regression of unclear etiology. These presentations have variously been referred to as Down syndrome disintegrative disorder, developmental regression, depression, and catatonia in Down syndrome. YM was a 21-year-old female with Down syndrome presenting with loss of skills and language, response to internal stimuli related to a popular television show, and slowed motor movements after a major life stressor. Her work-up included laboratory assessments; neuroimaging studies; and consultations by developmental pediatrics, neurology, and pulmonology. With no identified medical cause of her decline, she was referred to psychiatry and started on sertraline and risperidone. A few months after starting psychiatric medication, she began weekly individual psychotherapy. Within 18 months of starting treatment, she was functioning at her previous baseline, with no residual symptoms. Unexpectedly, 2 years after the onset of initial symptoms, YM experienced a second regression. The precipitant for this decline was not apparent, and she no longer responded to medication and therapy. However, she returned to her baseline functioning after approximately 12 sessions of electroconvulsive therapy (ECT). YM's case is different from many of those previously published, as she was high functioning and articulate prior to her regressions. Because of her verbal skills, she was able to offer some insight into her internal experience. Her relapse following complete resolution of symptoms is another distinguishing characteristic of her clinical course. YM's history underscores the challenges in developing a protocol to address developmental regression in DS as the variation in symptoms and contributing factors necessitate an individualized treatment plan.

Down syndrome (DS) is the most common genetic disorder in the United States, present in approximately 1 in 691 live births.[1] Individuals with DS are known to exhibit different behavioral and psychiatric phenotypes across the lifespan. Younger individuals exhibit more aggression and defiance, whereas adolescents and adults tend towards internalizing symptoms, including social withdrawal and depression.[2] In a recent evaluation of psychiatric diagnoses among adolescents and young adults with DS compared to other intellectual disabilities, individuals with DS were more likely to experience psychotic and depressive symptoms than their counterparts.[3] There are reports in the literature of young adults with DS experiencing developmental regression, but not all of them appear to fit into the broader definitions of depression and psychosis. Literature on this topic is sparse, primarily case reports about 1 or a few individuals. There are overlapping symptoms present in the majority of cases such as motor slowness, facial grimacing or tics, increased self-talk and social withdrawal, and lack of spontaneous expressive language production.[4] Presentation variability has resulted in cases being defined differently among providers (Down syndrome disintegrative disorder,[5] developmental regression,[6] depression,[7] or catatonia).[8] These different conceptualizations may contribute to conflicting rates of reported psychopathology amongst individuals with DS and

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evolving understanding of contributing factors in regression.

Due to the known association of DS and development of neurofibrillary plaques, regression has been hypothesized as an early manifestation of Alzheimer's disease (AD). Symptoms that may predate the development of dementia include sadness, sleep problems, and general regressive behavior.[9] In their report of acute neuropsychiatric disorders in adolescents with DS, Akahoshi et al found that when compared with adults with DS without regression, neuropathological changes characteristic of AD were present earlier.[10] There is also a case report in the literature of an adolescent boy with DS and regression successfully treated with donepezil, a medication traditionally used to treat AD, in combination with an SSRI. However, most episodes of regression in children and adolescents resolve completely with treatment, which would not be expected if the regression were a precursor to dementia.

Medical factors such as autoimmunity, hormonal shifts, and exposure to anesthesia may play a role in the development of regression. Worley et al report on a series of 11 children and adolescents seen over a 10-year period with regression. They suggest a new term, "Down syndrome disintegrative disorder," to describe the phenomena of autistic regression, cognitive decline, and insomnia seen in their case sample. They note that Down syndrome disintegrative disorder is different from a typical autistic regression in children with DS based on age of onset, female predominance, and associated insomnia. The majority of patients in their sample (91%) also showed elevated thyroperoxidase antibody titers compared to 23% of age-matched controls with DS without regression. Based on this finding, they suggest that Down syndrome disintegrative disorder may be linked to autoimmunity.[5] The onset of menarche has been noted in a number of cases as a precipitant to regression. However, resolution of hormonal imbalances alone has not resulted in return to baseline functioning. Exposures to surgical stress causing neuroinflammation and anesthesia causing the depression of cholinergic transmission have also been postulated as risk factors for regression.[4]

The majority of cases in the literature implicate life stressors as contributing to regression. For example, Stein et al reviewed the case of a 13-year-old female with DS, developmental regression, and depression. Her decline occurred in the context of moving homes and changing classrooms. They propose that behavioral problems could be a form of communication in an individual with minimal expressive language. This patient was also diagnosed with obstructive sleep apnea and her regression coincided with menarche. She exhibited improvement with a combination of antidepressant medication, continuous positive airway pressure for her sleep apnea, and increased psychosocial supports.[6] Other noted life stressors in the literature include a death in the family, change in living environment, change in family constellation, and different work and/or school expectations.[4]

Ghaziuddin et al described the histories of 4 adolescents with significant symptoms of regression without clear medical etiology. In each of the cases, regression was characterized as catatonia, manifested by change in motor activity (reduced or less often increased motor activity), unusual movements (stereotypies, grimacing, freezing, ambitendency, infrequent blinking, motor or vocal tics, posturing, automatic obedience), changes in speech (reduced meaningful speech; mutism; echolalia; "verbigeration," or senseless repetition of words and phrases; increased latency), changes in oral intake (reduced appetite and/or slowing down of food intake), decline in activities of daily living, bladder or bowel incontinence, negativism, and disruptions in cognition. Some of the cases also had symptoms of depression and psychosis, but none responded significantly to antidepressant or antipsychotic treatment, and in one individual, there was concern that such medications made things worse.[8] In a separate case report, Ghaziuddin and Jap reported on 2 other cases of adolescent females with DS and catatonia.[12] All of the cases from the 2 articles showed symptom improvement with either benzodiazepines and/or electroconvulsive therapy.

Case History

First Regression

YM was a 21-year-old female with Down syndrome, previously considered high functioning, urgently referred for psychiatric evaluation due to a 4-month episode of cognitive and behavioral regression, including loss of language, slowed motor movements, internal preoccupation, and concern for psychosis. These symptoms developed after YM moved away

from home to attend a special out-of-state college program for individuals with developmental disabilities in the fall of 2013. Prior to her regression, YM was described as "extremely sharp and quick." She was independently motivated to engage socially and manage interactions on her own and had never required mental health care.

When she returned home for Thanksgiving break in 2013, YM's parents noticed some minor declines in her functioning. She was less engaged, and mumbled and laughed to herself more often. However, her parents felt she was "okay," despite some worry about this change in her presentation. Their concerns abated somewhat after speaking to staff at the college. By December 2013, YM exhibited a significant decline in functioning. She barely responded to or engaged in interactions and conversation. She was "in her own world," frequently laughing to herself. She regressed in her ability to communicate, could not coherently formulate her thoughts, and struggled to manage all activities of daily living. Additionally, she experienced a significant increase in self-talk and social withdrawal. Her self-talk revolved around a television show for young adults involving popularity, murder, conspiracy, and deception. She identified herself as a character in the show and struggled to separate herself from the reality she created. Facial grimacing and nasal snorting were noted, in addition to slowed movements. Later in treatment when thinking about her initial regression, YM stated, "In the middle of the day my brain is too foggy, so I have to make a face."

In January 2014, YM's parents contacted a hospital-based clinic for individuals with Down syndrome asking for an evaluation of their daughter's regression. YM's primary care physician had examined her and, unable to uncover a medical cause of her symptoms, referred her for additional assessment. At the Down syndrome clinic, a developmental pediatrician evaluated her. YM was unable to socialize and attunement to her environment suffered greatly. During the session, between long periods of blanking out, YM described her thinking as "fuzzy." She vaguely articulated feeling stressed and overwhelmed at college. Her parents had been unaware of the level of her distress, but knew that she was spending a lot of time on homework, had minimal socialization with her peers, and forgot to eat most days. She spent all of her extra time watching a popular television show for young adults. Laboratory tests were ordered which, other than a slightly low ferritin level, were within normal limits. The pediatrician started YM on sertraline, a selective serotonin reuptake inhibitor. Melatonin was also introduced to help with ongoing sleep issues. Her parents were instructed to keep her engaged and to avoid any exposure to the television show on which she was fixated. YM initially showed minor improvements. However, after about 6 weeks of sertraline treatment she started to deteriorate. She developed abnormal movements and was more socially withdrawn and internally preoccupied. Due to her lack of sustained improvement, YM was referred for mental health services.

YM had a history of obstructive sleep apnea, diagnosed years earlier. She had a tonsillectomy and adenoidectomy at age 6 and repair of a submucosal cleft at age 12. Continuous positive airway pressure treatment (CPAP) was recommended in 2009. She was compliant with the intervention for a few years, but then stopped, complaining that it was uncomfortable and that the air leaked into her eyes. YM's parents also said her sleep symptoms, such as snoring, had resolved, thus she had not used CPAP for 2 years prior to her 2013 decline in function. Her family noted a major change in YM's sleep patterns when she returned from college in December 2013. She took hours to fall asleep due to constant self-talk, woke up several times during the night, and needed help from her mother to fall back asleep. Melatonin was helpful in managing sleep issues, but a repeat sleep study showed continued symptoms of obstructive sleep apnea. Due to the impact of obstructive sleep apnea on cognitive function, CPAP compliance became a key treatment goal.[13]

On initial evaluation with psychiatry, YM responded minimally to direct questioning. She appeared dishevelled and internally preoccupied, evidenced by slumped posture, matted hair, and food stains on her clothes. She was moving her lips as if talking to herself while averting her gaze. YM was oriented to name and place, but not time. On occasion, she giggled inappropriately. Her mother explained that she was running episodes of a popular television show through her head and that she believed she was one of the characters. She cooperated with having her vital signs checked, but walked slowly back to the office. She exhibited abnormal physical movements including

scrunching her face, sniffing dramatically, looking up, and pushing out her lips.

Because of the concern that she deteriorated after her dose was increased, the psychiatrist decreased YM's sertraline. Risperidone, a second generation antipsychotic medication, was added targeting psychosis. Based on presenting concerns, the timeline of deterioration, and the lack of obvious medical etiology for her symptoms, YM was diagnosed with an unspecified depressive disorder with psychotic features. Symptoms of depression included low mood, social withdrawal, lack of interest and motivation, decreased appetite, and poor sleep. Symptoms of psychosis included internal preoccupation and belief that she was a character in a television program. YM also met diagnostic criteria for catatonia, but this diagnosis was only considered after doing a literature review for cases with similar presentations. After showing some slight improvements with medication, YM began individual therapy. Due to YM's significant periods of blanking out with no response or ability to follow the conversation, sessions were limited to 30 minutes once per week. Appointments targeted increasing engagement and strategies for tracking conversations. She participated in multiple community activities and therapies for individuals with developmental disabilities. Prior to her regression, YM never needed involvement with disability services, so this was a new area for her and her family to navigate. The family had a difficult time keeping YM engaged at home. Use of a written schedule, journaling, and scheduled breaks for self-talk were suggested. At the onset of therapy, YM gave generic responses to make it seem like she was following the conversation. In therapy, she was taught how to request help or clarification when she blanked out or her thinking became "foggy."

Although YM showed improvement with psychiatric intervention and resumption of CPAP, because of the severity of her presenting symptoms, additional medical work-up was suggested. This included an MRI and EEG, both of which were normal. After a few months of medication and psychotherapy intervention, YM self-reported, "I'm becoming myself again." She was able to engage in meaningful back and forth conversation and was less internally preoccupied. Over time, YM was more able to advocate for herself.

As YM's ability to follow conversations and answer direct questions improved, psychotherapy sessions focused on addressing distorted thinking and using strategies for remaining present-focused. Even early on, during moments of clarity, YM was able to self-reflect through art. In describing one of her paintings she said, "I feel kind of dark inside. The past mistakes are coming out now." Appointments continued weekly, but the duration increased to an hour. YM's level of insight increased exponentially. Despite the improvements in her regression and psychosis, she looked more depressed. She stated, "There is a lightness and brightness in my brain and forehead combined with the fogginess. It is painful to think." Her sertraline was increased targeting "mental fogginess" as a manifestation of depression. In March 2015, tapering of her risperidone was initiated due to side effects of weight gain and sedation.

YM was eventually able to engage in discussion about her distorted thought process and depressive symptoms. She articulated a desire to be more like the main characters in the television show that had preoccupied her, who are beautiful, thin, and popular. Themes of perfection were also noted. YM shared that despite wanting to be like many of the characters in the show, she related most to a different character who she perceived as being bullied and rejected. Over time, YM's improvements allowed her to articulate the internal struggles she experienced when moving away from home. She felt she had to rely on herself, rather than finding support from friends and family. She stated, "When you are in a new town or a new place, you kind of feel invisible. It is hard to be independent without your family." YM's family shared insight into small changes in her motivation to interact, her ability to focus on the content of communications, and her humor. Prior to her initial regression, YM was described as funny and engaging. The re-emergence of these traits served as a barometer of her improvement. YM was better able to identify when she was engaged in her television-based internal narrative, which allowed for more accurate assessment of improvement and decline in functioning.

Second Regression

In mid-November 2015, YM's family began noticing some minor differences in her behavior. She forgot to do things like shutting the car door after exiting, lost her train of thought during conversations, and had brief moments of withdrawing into her own world.

Over a period of 2 weeks, YM's periods of withdrawal increased significantly and she needed prompting for all activities of daily living. She could not dress herself without support, experienced a decrease in appetite and energy, and struggled to follow simple single-step directions. She was unable to write her name or state her last name. Direct questioning resulted in incongruent responses. For example, when asked how she slept the night before, she responded, "There were 5." Her mother speculated that she was again running episodes of the television show through her mind and was responding to the scenes. Her mother later discovered that YM had watched part of an episode on November 21st, 2015, just before her second regression.

Medical etiologies were again investigated, but there was no identified explanation for her deterioration. Symptoms remained consistent with depression and psychosis. In addition, YM met diagnostic criteria for unspecified catatonia. Over the next 3 months, adjustments to her sertraline and risperidone did not result in significant improvement. The patient attended therapy appointments twice per week with the goal of keeping her engaged and grounded in reality. In contrast to her previous psychotherapy treatment, she struggled to participate in a meaningful way. She could answer 1 or 2 concrete questions, but then would begin to self-talk loudly without any acknowledgement or recognition of the therapist being in the room. She laughed to herself and made bizarre statements. Interjection into the conversation by the therapist did not result in self-awareness or change in behaviour. Despite having come to therapy in the same location for over a year, YM often became confused about where she was going and the risk of YM wandering off became problematic. Her symptoms were tracked closely, but she showed no improvement. The psychiatrist added low dose lorazepam for insomnia with slight improvements. Due to her history of obstructive sleep apnea, she was briefly medically admitted for pulmonary monitoring during a trial of lorazepam up to 11 mg daily targeting catatonia. Her sertraline and risperidone were discontinued. Although she tolerated the lorazepam medically, she was more confused and less verbally responsive to direct interaction. The psychiatrist tapered her off the lorazepam and started a course of electroconvulsive therapy (ECT).

After 4 ECT treatments, YM showed moments of lucidity. In biweekly therapy sessions, she was better able to track the conversation and answered a few more questions. Improvements were noted on the mini mental status exam, but she was only able to focus for a maximum of 30 minutes. After 30 minutes, YM would often ask to go to the restroom. The therapist and YM's mother would hear her loudly talking to herself in the restroom. The content remained bizarre in nature, but YM was able to re-engage in therapy for a short period once she returned from the bathroom. Even when she was aware that others had heard her self-talk, she was not able to discuss it further. Her symptoms of regression resolved completely after 12 ECT treatments (3 times weekly), and she functioned at her pre-regression baseline. With the more abrupt resolution of her symptoms, YM was only able to reflect on her regression as relayed by family members and providers. She started maintenance ECT and was treated with low dose lithium carbonate based on her history of mood symptoms. YM does not recall any details of her regression and refers to it as her "sickness." She has a difficult time understanding what happened and has expressed sadness about the time that she lost and the many events she missed out on while she was ill. She often mentions that everyone "moved on with their lives" without her.

Discussion

Within the last 10 to 20 years, there has been increased focus on regression in Down syndrome. Various etiologic hypotheses have been noted in the literature, including autoimmune phenomenon and psychosocial stressors. In the case of YM, the distance from previous support and scaffolding, increased academic expectations, and high internal drive to succeed in a new setting resulted in social withdrawal, disruption of sleep patterns, poor hygiene and food intake, and obsessive thoughts about perfection. Initially, YM's disconnection from reality prevented her from sharing the intricacies of her college experience. Cognitive-behavioral therapy in conjunction with medication management allowed her to develop insight into how this experience was overwhelming. Despite this insight, YM's internal drive for self-reliance and independence likely contributed to her relapse. Her case offers insight into regression triggered

by psychosocial stressors at a level not previously discussed within the literature.

YM's initial response to psychiatric medication is consistent with many reported cases. Most patients show improvement with some combination of antidepressant and antipsychotic medication. For patients who do not respond to medications and who meet diagnostic criteria for catatonia, more intensive intervention, such as high-dose benzodiazepines or ECT, may be required. It is not understood why YM initially had complete resolution of her symptoms with medication, only to relapse. Consistent with other case reports, YM improved with ECT after failing medication interventions.[8]

Findings from this case study support a multimodal approach to addressing regression in Down syndrome. Psychiatric medication; therapy; and intensive, active involvement in community activities resulted in an initial return to baseline functioning for YM. YM's second regression was not triggered by an identifiable psychosocial stressor and the treatments that had been effective for the first regression proved ineffective, requiring the introduction of new therapeutic approaches (eg, electroconvulsive therapy). She has again shown complete resolution of symptoms with this new approach. Some professionals in the Down syndrome community have reported multiple regressions in an individual, but there is no literature to describe this phenomenon.[14] Review of the literature supports an individualized approach for assessment and intervention in similar cases, as symptom overlap does not guarantee the same response to treatment. While regression in Down syndrome continues to be poorly understood, YM's case illustrates the need for frequent evaluation of functioning during times of transition and potentially increased stress. At this time there is no protocol to prevent regressive episodes, but improved identification and description could lead to development of preventive strategies.

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A Multidisciplinary Approach to the Treatment of Comorbid Neurodevelopmental and Medical Problems

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Case Presentation

Jack is a 10-year-old boy with a history of lye ingestion at 18 months, which resulted in esophageal stenosis, vocal cord paresis and dysphagia, aspiration syndrome, and jejunostomy tube (J-tube) placement. He had regular swallow studies over the years subsequent to his ingestion, and started feeding therapy with a speech and language therapist at age 10 while J-tube dependent. Jack had attended outpatient psychotherapy for anger and behavioral concerns for the year prior to presenting for current treatment. A pediatrician had prescribed a stimulant medication for symptoms of attention deficit hyperactivity disorder (ADHD) since age 5. One year before the time of evaluation, the pediatrician had discontinued methylphenidate due to weight loss, which became a primary health concern as his low BMI placed him in failure to thrive range (BMI<1st%ile). In addition to his medical risk, Jack demonstrated significant impairments across physical, social, psychological, and school functioning, which prompted a referral to the Medical Day Treatment (MDT) program by his pediatrician. The MDT program is a partnership between a children's hospital and school district to provide classrooms utilizing the district's curriculum within a treatment setting housed in the behavioral health section of a children's hospital. The program's services include a nursing team to provide medical supervision and daily medical care, teaching staff from the school district, and a mental health team including psychotherapists (licensed clinical social worker, clinical psychologist, and postdoctoral psychology fellow), milieu support staff, and a consulting psychiatrist.

At the time of enrollment, Jack was not completing his J-tube feeds at home because it was difficult for his mother to manage his refusal behaviors, which were associated with fears that his J-tube would disconnect in the middle of the night, since that occurred in the past. Jack had completed fourth grade and had an individualized education program (IEP), which included speech therapy, occupational therapy, reading services, and psychological support. Jack presented to the intake with the prior diagnosis of ADHD (noted above), as well as symptoms of depression (sadness, irritability, frequent crying) and anxiety (fears, worries, separation anxiety). His mother stated Jack also exhibited frequent anger, irritability, and school refusal behaviors (eg, crying every morning). She described him as having long-standing difficulties with peers, including no identified friends and experiencing increased teasing over the prior year. Jack lived with his mother and 3 siblings (16-year-old sister and 12-year-old twin sisters, one of whom was severely disabled). Jack's 12-year-old sister had severe physical impairments due to cerebral palsy, which required constant care by his mother. His mother was unemployed and had no outside support from her family. Jack's mother also reported her own history of learning disabilities and mental health problems.

During the initial evaluation, Jack, who was holding a stuffed animal, appeared highly anxious and did not verbally respond to the interviewer. When he did verbally respond, his answers did not match the question or content of the interview and he expressed worries he would continue to be teased at MDT. His responses to the Revised Child Anxiety and Depression Scale (RCADS)[1,2] suggested clinically-significant levels of separation anxiety, generalized

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anxiety, panic, social phobia, and depression (refer to Table 1 for results).

Based on the reasons for the initial referral and results of our assessment, treatment goals focused on improving caloric intake, addressing anxiety and depression, improving peer relationships, and decreasing impulsivity in the classroom. The psychotherapist coordinated with the nursing team to address barriers to increasing caloric intake and weight gain. The team developed a system to track progress by implementing weigh-ins twice a week and documenting the percentage of food intake at breakfast and lunch. The team recommended changing the timing of J-tube feeds to the evening with video games to address his fear of overnight feeds, and Jack cooperated with this new schedule. A fixed-ratio reinforcement schedule implemented in the program and at home included rewarding increased food intake in order to build more positive associations with the eating experience.[3,4] This behavioral approach also targeted Jack's fear of choking through exposure and relaxation training. At home, Jack earned marbles in a jar when he completed his feeds and then exchanged the marbles for a videogame. During this time, the psychotherapist provided education to Jack's mother, the nursing team, mental health counselors, and teachers regarding effective behavior-management techniques, such as contingency management and use of positive reinforcement.[5] Jack was also taught emotion-regulation skills to decrease tearfulness and tantrums during meal times and feeds. Finally, collaboration with the pediatrician resulted in the utilization of home nursing support in order to facilitate consistent feeds at home and provide greater support to Jack's mother.[6]

Prior to admission to MDT, Jack had been prescribed methylphenidate (patch and liquid formulations) starting around age 5 years old. He had stopped taking the stimulant medication approximately 1 year prior to presenting to MDT, due to concerns by his pediatrician about low appetite and weight loss. However, feeding difficulties did not resolve with discontinuation of the stimulant and he did not gain weight. Jack's first psychiatric evaluation occurred within 1 month of admission to MDT. Weight concerns (BMI<1st%) and a reported inability to swallow pills dictated initial medication choices. Stimulants were not an option and atomoxetine does not come in liquid formulation. Given concerns about both anxiety and poor food intake, the first psychiatrist recommended low dose dispersible olanzapine 2.5 mg at bedtime and mother provided consent. Although olanzapine is not considered first-line treatment for anxiety and does not have an indication for feeding disorders in children, mother reported that olanzapine was beneficial for anxiety, sleep, and weight. It is possible that improvements in symptoms could have resulted from either his participation in the program or start of medication, or a combination of both.

While there was improvement in Jack's emotion regulation, he continued to demonstrate unusual behaviors such as repeating the same random word in response to all questions and responding to social cues inappropriately (eg, laughing in response to his peers' expressions of sadness). He struggled to develop appropriate peer relationships, exhibited communication difficulties, and continued to demonstrate food refusal behaviors and early satiety, leading to no improvement in his BMI. To evaluate if these concerns could be related to a possible developmental disorder, Jack was referred for an Autism Spectrum Disorder (ASD) evaluation. This evaluation included the administration of the Social Communication Questionnaire, Lifetime (SCQ)[7]; the Social Responsiveness Scale, Second Edition (SRS-2)[8]; and the Autism Diagnostic Observation Schedule, Second Edition, Module 2 (ADOS-2)[9]; as well as a developmental history interview with the mother, and a classroom observation of the patient.

Responses on the SRS-2[8] indicated perceived severe deficiencies in reciprocal social behavior that resulted in moderate interference in everyday social interactions (Total Score, T-score: 75). Such scores are typical for children with a diagnosis of an ASD of moderate severity. Responses on the SCQ[7] indicated significant perceived difficulties in social communication that were also consistent with a diagnosis of an ASD. The administration of the ADOS-2 was modified on the basis of his language level and developmental age. Based on the standardized protocol of the ADOS-2, he was administered Module 2 (Phrase Speech) instead of Module 3 (Fluent Speech, Child/Adolescent). He displayed several communicative strengths during the ADOS-2 administration, including the use of communicative gestures (eg, pointing) and response to the examiner's questions. His areas of weakness included difficulty initiating and maintaining a conversation

(ie, conversation occurred only when he was asked a question and did not elaborate), a noticeable lack of eye contact, few social overtures, and communication mostly to request items or assistance from the examiner. No restricted and repetitive behaviors were observed during the ADOS-2 administration, however, hand flapping and repetitive finger movements were noted during the classroom observation.

Jack's overall Total score on the ADOS-2 Module 2 algorithm for children aged 5 years or older was consistent with an ADOS-2 Classification of autism (specific ADOS-2 scores are not reported as per the manualized recommendations of the ADOS-2). His ADOS-2 Comparison Score further indicated that on the ADOS-2, he displayed a moderate level of autism spectrum-related symptoms as compared with those who are classified as having ASD on the ADOS-2 and are of the same chronological age and language level. Based on these findings, cognitive behavioral interventions were modified to address social and communication deficits associated with autism.[10]

To address depression and anxiety, Jack participated in role plays about how to effectively express his emotions. He was introduced to step-by-step emotion regulation strategies to use when becoming dysregulated, and visual cues were placed throughout his classroom to remind him to use these strategies. And while Jack showed moderate progress in emotion identification and expression, he struggled with applying his skills learned in therapy to the classroom due to impulsivity and inattention. Given this, a psychiatric evaluation was requested.

Jack was evaluated by the new MDT psychiatrist consultant for ongoing concerns about ADHD symptoms as evidenced by the teacher Vanderbilt[11] results (inattention and hyperactivity both 9/9). At the time, Jack continued to take olanzapine dispersible tablets. The psychiatrist discussed treatment options for ADHD with both mother and the pediatrician, who supported the use of either an alpha 2 agonist or a stimulant given that Jack's weight could be closely monitored in the program. The patient was started on guanfacine, which was titrated slowly to 0.5 mg twice a day over a 2-month period (the initial titration was slow because it was unknown if Jack would be consistently able to swallow pills, but he ultimately was able to swallow the medication without difficulty). Vanderbilt assessments suggested some improvement in ADHD symptoms, though they continued to be in the diagnostic range for ADHD. (Teacher scores-inattention 6/9 and hyperactivity 7/9, and parent scores-inattention 2/9 and hyperactivity 6/9.) Guanfacine was changed to a slow release version guanfacine SR (1 mg) to improve coverage. After the change to guanfacine SR 1 mg, Jack's mother noted a more marked improvement in symptoms, including increased focus and decreased hyperactivity. Jack's psychotherapist also reported benefits, including Jack's improved ability to respond to redirection and increased participation in program activities.

Jack had a break in medication management due to an insurance interruption that impacted access to psychiatric services billed to insurance, but not Jack's enrollment in the MDT program*. During this time, the family was unable to obtain his medications for about 1 month; guanfacine SR and olanzapine were therefore discontinued and Jack's sleep and behaviors worsened. Once insurance was re-instated, mother consented to restarting 1 medication at a time, beginning with guanfacine SR 1 mg daily. Jack's mother reported that Jack's listening abilities improved and he responded well to redirection. Olanzapine was not restarted since anxiety had decreased and there was no clear indication for the medication.

In individual psychotherapy, behavioral strategies such as practicing impulse control and regulating emotional responses were used to support the positive effects of medication. Jack showed an improved response to learning skills, and new behavioral recommendations were made both to the teacher to implement in the classroom, and to his mother to implement in the home.[12,13] These recommendations focused on the use of praise, simplifying expectations into small steps using visual cues, and reducing distractions.

Although Jack's emotional and behavioral functioning improved with these interventions, he continued to struggle with gaining weight. Jack's psychotherapist reported concerns about Jack's continued weight loss and mother's ability to ensure Jack was consuming sufficient calories at home to the Department of Social Services (DSS). DSS assigned a care coordinator to work in the home and to assist Jack's mother with

*MDT receives funding from the state budget and does not receive direct reiumburesment from Medicaid; this allows for MDT services to continue during a temporary disruption in insurance coverage.

navigating the healthcare system. Prior to DSS involvement, Jack's mother communicated with the treatment team about her own mental health challenges, which seemed to interfere with implementing behavioral approaches in the home and limit the patient's weight gain. After DSS became involved, mother began her own mental health treatment. The treatment team continued to work with the DSS coordinator, who regularly attended treatment meetings with the mother. The coordinator served as a bridge between the program and home, and was able to help Jack's mother follow the recommendations made by the team. As a result, Jack's mother was able to implement recommendations made by the team, including behavioral strategies to manage problem behaviors during feeds.

This multidisciplinary team approach to assessment and treatment yielded substantial improvements across areas of Jack's functioning: school, social, emotional, behavioral, and health. The patient presented to the treatment program with concerns related to school refusal, failure to gain weight, social relationships, and emotional and behavioral symptoms. Jack's school refusal behaviors immediately extinguished, with 98% attendance in the treatment program during the school year and over the course of 2 summer programs. His mother reported that he showed no refusal behaviors or separation anxiety, getting ready in the mornings with high cooperation and no need for encouragement. Jack also responded well to a fixed ratio reinforcement schedule implemented to increase medical adherence. His food intake on the unit increased from one-quarter of breakfast and one-half of lunch to one-third of breakfast and three-quarters of his lunch, and he consistently drank his meal supplement twice a day without challenging behaviors. Jack's BMI increased from 13.1 (<1st%) at intake to 14.4 (2nd%) at 15 months; this indicated a weight increase of 11 pounds. Notably, his BMI peaked at 15.2 (12th%) at almost 6 months into treatment and weight fluctuations have been documented over the course of his 15 months of care.

The RCADS[1,2] and the Peds Quality of Life (PedsQL)[14] were administered at intake and at the end of the school semesters to assess symptoms and monitor treatment outcomes (at 7 and 15 months post intake). The PedsQL Family Impact Module (PedsQL FIM),[15] a validated measure of parent and family functioning, was not part of the intake assessment battery, but was used at other time points during treatment to assess parent and family functioning. Overall, these results indicated that Jack had a significant decrease in anxiety and depression from the clinical range at intake to the normal range in most domains 7 months later, with improvement sustained at 15 months. Jack's functioning and quality of life also appeared to substantially improve across areas, with 15-65 point increases for self-report, and 9-100 point increases for parent-report (the parent rated her child as a 0 for emotional and school functioning at intake; she rated him at 100 for these same areas 15 months later). Results on the PedsQL substantiate observations of improvements emotionally, socially, and in school. Scores on the Peds QL FIM also indicated improved parent and family functioning across all but 1 area between 7 months and 15 months. Please see Table 1 for further details.

Discussion

Children with feeding difficulties often struggle to maintain a healthy weight. Feeding disorders, including avoidance restrictive food intake disorders, are common in children diagnosed with neurodevelopmental disorders, but they can also develop as a result of environmental or biological factors.[16] The existing literature suggests using psychiatric medications, positive reinforcement, and cognitive behavioral therapy for children who have developed feeding difficulties after a medically-traumatic event. Distraction and exposure techniques are recommended for children with an organic cause to their feeding difficulties.[4] A comprehensive and effective treatment plan is essential in treating feeding disorders, since chronic feeding difficulties can lead to suboptimal growth, social deficits, nutrient deficiencies, and poor academic progress.[6] Although the literature provides this guidance for feeding disorders, Jack showed minimal response to these interventions, indicating a more complicated diagnostic presentation. Indeed, Jack demonstrated both organic (dysphagia and aspiration) and behavioral (failure to thrive) aspects to his feeding disorder in the context of other serious medical, psychiatric, and psychosocial challenges, underscoring the need for a multidisciplinary approach to treatment.

Jack's treatment course highlights how valuable a thorough assessment process can be in identifying

factors that were previously not identified or addressed in standard approaches to treating feeding disorders. Jack had participated in multiple interventions and evaluations through school prior to his enrollment at Medical Day Treatment, however, his ASD remained undiagnosed. Information from Jack's ASD evaluation helped shape interventions targeting treatment goals to develop age-appropriate social skills, manage peer relationships, and improve feeding behaviors. Jack's developmental level and cognitive, social, and emotional skills were used to set realistic goals in treatment, and they were modified based on Jack's readiness and ability to learn a new skill or behavior. Jack may not have demonstrated treatment gains if the treatment interventions were not modified based on his diagnoses and developmental level. Providers should consider comprehensive medical and psychological evaluation and re-consider interventions used in sessions if symptoms persist after participation in evidence-based treatments.

Jack's psychiatric comorbidities became a central focus of his multidisciplinary treatment and are worthy of further discussion. ASD is a neurodevelopmental disorder affecting approximately 1% of the population and is often comorbid with feeding problems.[17] Behaviors associated with feeding disorders and ASD, including food refusal and avoidance, can have significant negative impacts on the child's health and the parent-child relationship. These behaviors in children with ASD may be the result of sensory, behavioral, or social impairments and are treated with behavioral interventions.[6] One of the key behavioral influences of ASD on feeding difficulties may be symptoms of repetitiveness, rituals, and hyper- or hyposensitivity to sensory input aspects of the disorder. Children diagnosed with ASD may have specific rituals associated with meal preparation and meal times. Additionally, children diagnosed with ASD have higher rates of gastrointestinal distress, which may play a role in the development of feeding problems. However, the relationship between feeding, ASD, and medical diagnoses have not been parsed out in the literature. Since this is the case, a multidisciplinary approach to treatment, at a developmentally appropriate level, is critically important.[6]

In addition, ADHD and anxiety are highly comorbid with ASD,[18] adding complexity to psychiatric and behavioral symptom presentation for a child with feeding difficulties. Children with comorbid ADHD and ASD demonstrate higher rates of problems with inhibition and greater severity of ASD symptoms than children with ASD alone.[19, 20] The comorbidity of medical and neurodevelopmental conditions requires careful evaluation and coordination across providers to optimize therapeutic interventions. In Jack's case, ADHD treatment had been limited by concerns of weight loss and feeding/swallowing difficulties that initially limited medication choices. Psychostimulants associated with an increased risk of appetite suppression in children with ASD, similar to the rate in typically developing children.[21] A recent study reported that extended release guanfacine was efficacious for decreasing hyperactivity and impulsivity in children with ASD, suggesting it is a reasonable alternative to stimulants in children with ADHD, ASD, and feeding problems.[22] Indeed, this case illustrated negative outcomes of untreated ADHD, including a decline in behavioral functioning that negatively impacted academic and social functioning. The addition of medication to target ADHD symptoms of impulsivity and inattention that did not suppress Jack's appetite allowed the treatment team to implement behavioral and cognitive behavioral strategies to address other medical and psychological symptoms.

Identification of barriers to treatment and implementation of a plan to address barriers to treatment is as important as any therapeutic intervention in complex pediatric cases,[10] and the multilidisicplinary team's ability to address the challenges in Jack's home environment were particularly critical for his treatment. While DSS involvement is often resisted by families due to negative misperceptions and feelings of disempowerment, it was critically important to addressing the challenges Jack's mother faced in managing his complex medical and psychiatric problems.[23] Feeding difficulties can be a substantial burden for families, especially in single caregiver homes with multiple children with special health care needs. Providers should become familiar with the organizations and services available to families and use those resources to help bridge the gap between office and home. This case also exemplifies the importance of using a range of methods to evaluate progress and outcomes, including scores from validated measures, observational data, and objective metrics.

Conclusion

Jack's successful treatment involved the use of multiple intervention modalities, the work of a skilled multidisciplinary team, and the development of a system of care. Also critical was the sustained engagement of this team and system over a 15-month period, which was necessary to realize meaningful progress. This collaboration of medical care, psychological treatment, psychiatric consultation, family support, schools, and community resources models the ideal approach to a patient suffering from medical, emotional, academic, social, behavioral, and familial challenges. Each intervention may have had some success in isolation, but it is likely that their combination resulted in synergistic effects, and greater and more sustained improvements than would have been achievable with a less integrated approach. The Medical Day Treatment model is uniquely capable of the coordinated, multidisciplinary approach to assessment and ongoing treatment that patients like Jack desperately need if they are to move from pervasive functional deficits to thriving across domains of functioning essential to optimal development and positive outcomes.

Table 1. Psychological outcome measure results over time

	Intake		7 Months		15 Months	
	Parent	Self	Parent	Self	Parent	Self
RCADS						
Generalized Anxiety	70	74	51	49	35	45
Panic	51	73	41	50	45	55
Social Anxiety	75	84	43	45	35	47
Separation Anxiety	>80	78	>80	79	65	59
Depression	>80	84	69	66	72	50
PedsQL						
Physical	91	59	100	75	100	75
Emotional	0	40	50	55	100	60
Social	25	35	90	65	100	50
School	0	20	70	70	100	85
Total	37	41.3	80.4	67.4	100	68.5
PedsQL Family Impact						
Physical	N/A		42		75	
Social	N/A		6.25		37.5	
Emotional	N/A		60		100	
Cognitive	N/A		45		10	
Communication	N/A		25		50	
Worry	N/A		55		85	
Total	N/A		36.81		53.47	

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A Comprehensive Transdiagnostic Approach to Pediatric Behavioral Health

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Abstract

A transdiagnostic approach to children's behavioral health treatment "draws from a unifying theoretical model that explains disparate conditions via common underlying mechanisms."[1] Transdiagnostic behavioral health interventions have gained increasing attention for their potential to better address the reality of complex, highly-comorbid diagnostic presentations and enhance the dissemination and implementation of evidence-based practices. While significant gains have been made in the adult-focused transdiagnostic literature, further delineation of a pediatric transdiagnostic approach is warranted. This paper highlights key transdiagnostic mechanisms that have been associated with both internalizing and externalizing pediatric behavioral health problems (eg, parenting, sleep regulation, emotion regulation, information processing biases, and experiential avoidance), and reviews the current state of the literature on transdiagnostic assessment and intervention. Initial efforts to develop and implement a new transdiagnostic clinical program designed to more effectively address the behavioral health needs of children and adolescents, improve the dissemination and implementation of evidence-based treatments, and address key weaknesses in the pediatric transdiagnostic literature are then described. The first stage of the program has focused on developing tools to efficiently and effectively measure transdiagnostic mechanisms that underlie pediatric behavioral health, which will then guide clinicians in developing a modularized treatment plan that is individually tailored. This approach holds great promise in further elucidating the transdiagnostic mechanisms that underlie pediatric behavioral health problems and their effective treatment. Furthermore, these approaches may inform the development of a more targeted classification system for behavioral health problems and improve current assessment procedures.

In this paper, a *transdiagnostic* approach to assessment and intervention is proposed as a method to comprehensively address the complex behavioral health needs of individual children and adolescents. The term *transdiagnostic* is not yet widely understood in the field of psychotherapy research. It is best defined as an approach that "draws from a unifying theoretical model that explains disparate conditions via common mechanisms."[1] Here, the term *transdiagnostic* will be used to describe a clinical approach that reduces reliance on diagnostic categories for treatment planning. Rather, the proposed approach to transdiagnostic treatment is guided by a targeted assessment of the underlying mechanisms that drive and maintain identified behavioral, emotional, and social concerns.

A transdiagnostic approach to behavioral health may be particularly useful in addressing the reality of complex, highly comorbid clinical presentations. Lifetime prevalence estimates indicate that approximately half of those who meet criteria for a psychiatric disorder will also meet criteria for at least 1 other disorder, with most comorbid presentations having an onset in childhood or adolescence.[2] Researchers have made considerable progress in the development of evidence-based, transdiagnostic treatments for comorbid presentations in adult populations (eg, Barlow's Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders).[3] Among pediatric populations, the ability to concurrently treat comorbid presentations is arguably even more critical, given high rates of psychiatric

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comorbidities and developmental continuity across the lifespan. Results from a longitudinal community study of children ages 9 to 16 revealed considerable concurrent comorbidity, with 25.5% of children identified as having psychiatric comorbidities. For example, the odds of having an anxiety disorder among children who had a depressive disorder were 25.1 times higher for boys and 28.4 for girls when compared to children without a depressive disorder. And the odds of having oppositional defiant disorder among boys and girls who had a depressive disorder relative to those without a depressive disorder were 20.7 and 15.1, respectively.[4] Interestingly, heterotypic continuity (continuity from one diagnosis to another) was much stronger in girls than boys. For example, girls with anxiety were shown to be at higher risk for later development of substance use disorders.[4] In order to effectively treat and maintain therapeutic gains, clinicians must be able to diagnose and treat a child's primary presenting problem, as well as any comorbid concerns. For example, a child referred for concerns related to disruptive behavior may also demonstrate anxious avoidance, depressive symptoms, and/or sleep dysregulation. If these comorbid concerns are not addressed, treatment outcomes will likely be poor and short-lived.

The present paper argues that a comprehensive transdiagnostic approach to pediatric behavioral health would better address the complex needs of children, adolescents, and their families, while also providing opportunities to further investigate and understand the mechanisms that underlie emotional and behavioral difficulties. Limitations to current classification and treatment practices will be discussed, followed by a review of the state of the research on transdiagnostic approaches to pediatric behavioral health. Necessary future research directions will be introduced, including the need to improve transdiagnostic assessment methods and to expand transdiagnostic intervention approaches to include externalizing as well as internalizing presentations. Finally, current pilot projects designed to address the measurement of transdiagnostic mechanisms will be described. These projects have focused on developing assessment tools (eg, semi-structured interview, parent and child questionnaires) aimed at efficiently and effectively measuring pertinent transdiagnostic mechanisms associated with pediatric behavioral health.

Limitations to Current Classification and Treatment Practices

The limitations of the current diagnostic system for psychiatric disorders (ie, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSM-5)[5] are often discussed. A longstanding tension exists within this system, in which the need for a common and reliable language competes with the reality of complex, highly comorbid clinical presentations.[2] Intervention research based on the categorical approach to diagnosis, as delineated in the DSM, has resulted in evidence-based treatments (EBTs) developed for those individuals with clear, single-diagnosis clinical presentations. Unfortunately, these manualized treatments may be less effective for the many patients who meet criteria for multiple DSM diagnoses or experience subclinical impairment across multiple areas.[6] Further, manualization of treatments for specific disorders leads to training and dissemination challenges. It is not realistic to expect individual clinicians to attain competency in all available EBTs, nor is it cost effective for clinics to train staff on the growing number of diagnosis-specific interventions.[7] This training burden is particularly troublesome in light of evidence that, despite positive findings in highly-controlled efficacy trials, EBTs for youth are not necessarily more effective than usual care in real-world practice settings.[8]

Recent discussions in the field of psychotherapy implementation have argued against the continued proliferation of manualized treatments developed through efficacy trials and based on DSM categorical diagnoses, which are often underutilized and slow to be adopted in clinical settings. Within the traditional biomedical model of treatment development, it is estimated to take 20 years for a treatment to be considered efficacious and effective enough for broad dissemination.[9] Furthermore, few of the EBTs that make it through this rigorous validation process are ultimately taught in graduate programs or available to children and adolescents in public mental health settings.[10] This disparity between availability and utilization of EBTs is related to the numerous differences between efficacy trials and actual clinical practice. Compared to efficacy clinical trials, real-world practice settings are more likely to treat children and families with multiple problems, more heterogeneous clinical and demographic presentations, more severe psycho-

pathology, and greater functional impairment.[11] Compared to efficacy clinical trials, clinicians in real-world practice settings also carry higher clinical caseloads.[11] These differences may also help to explain the finding that, when tested against usual care, EBTs have demonstrated effect sizes that are small to moderate at best.[8]

Concerns regarding the effectiveness of DSM-based treatment also extends to DSM-based research. For example, the National Institute of Mental Health's (NIMH) recently released Research Domain Criteria (RDoC), which is designed to address this institute's assessment that the advances in basic and translational research based on a DSM categorical approach has stalled, and that a focus on underlying mechanisms may be a more effective approach to real advances in behavioral health research.[12] Briefly defined, RDoC is a dimensional research classification system that is rooted in behavioral neuroscience. Within the RDoC framework, diagnoses are based not only on clinical observation and patients' phenomenological symptom reports, but also on additional units of analysis (eg, imaging, genes, physiological activity, behavior) in order to better reflect the brain-behavior underpinnings of mental health.[12] Much research is needed to define these units of analysis so that they can better inform a diagnostic classification system that more comprehensively describes patients' clinical presentations and needs. The emerging challenge for clinicians is that the research base, which will result from RDoC, will no longer connect explicitly to the DSM. As such, it will be necessary to identify ways in which RDoC mechanisms can be measured and addressed in clinical practice. Continued dialogue between RDoC researchers and the developers of mental health interventions should result in EBTs that more comprehensively address the complexities of patients' behavioral health needs.

Transdiagnostic Mechanisms

With RDoC, the NIMH urges researchers away from studies that rely on current classification systems (DSM-5, ICD-10) and towards the study of mechanisms, especially those that are common across multiple disorders. These mechanisms may include biological processes (eg, sleep-wake cycles), as well as cognitive and behavioral processes (eg, attention, perception, social communication).[12] In line with the RDoC initiative, the transdiagnostic approach to behavioral health is thought to reduce emotional/behavioral concerns by intervening at the level of the mechanism (eg, emotion regulation, sleep disturbance), rather than at the level of the symptom (eg, tantrums, irritability). Mechanisms can be considered transdiagnostic when they influence the etiology and/or maintenance of multiple problem behaviors. As defined by Ehrenreich-May and Chu,[1] these mechanisms may exist on the intrapersonal level (eg, cognitions, behaviors, physiological processes), the interpersonal level (eg, parent-child relations), and on the community level (eg, cultural influences, neighborhood resources). Similarly, Nolen-Hoeksema and Watkins[13] describe mechanisms as either more distal (environmental, distant in time from presenting pathology) or more proximal (within-person, more directly involved in pathology).

Many distinct processes have been identified as mechanisms that underlie and maintain childhood psychopathology, making them appropriate targets for intervention. These include attentional dysfunction,[14] sleep,[15] and emotion dysregulation.[16] Additional intrapersonal processes worth considering include distress tolerance, rumination, attribution errors, self-efficacy, and experiential avoidance. Interpersonal mechanisms include parenting behaviors, peer victimization, marital conflict, abuse, friendships, family rituals, and parental psychopathology.[1] More distal, community-level mechanisms include poverty, exposure to violence, and protective cultural factors.[17] Consistent with Frieden's Health Impact Pyramid,[18] Hudziak and Bartels argue for the consideration of distal factors and factors that have not traditionally been the target of mental health assessment and intervention, such as religiosity, sports participation, stressful life events, and family conflict. At their Vermont Center for Children, Youth, and Families (VCCYF), Hudziak and colleagues aim to develop treatment plans that include not only traditional therapy but also "prescriptions" for wellness-related protective and preventive activities such as violin lessons, fitness regimens, and screen-time reduction.[19]

It quickly becomes apparent that innumerable processes could be described as transdiagnostic mechanisms. Ehrenreich-May and Chu caution against over-inclusiveness, emphasizing a balance between explanatory power and parsimony.[1] The advent of

RDoC should provide further clarification about how to strike this balance. In the interim, mechanisms that have been shown to impact a range of pediatric clinical presentations and that respond to clinical interventions should be considered for inclusion in the development of transdiagnostic clinical interventions. A review of the literature suggests that these criteria are met by the following mechanisms: (1) parenting practices, (2) sleep regulation, (3) emotion regulation, (4) information processing deficits, and (5) experiential avoidance. Each selected mechanism is described in detail below.

Parenting

Parenting behaviors have been implicated in the development and maintenance of a variety of pediatric behavioral health difficulties.[20,21] More specifically, interactions between a child's biological temperament and parenting practices that might be too harsh, permissive, and/or inconsistent increases the risk for developing unhealthy parent-child interactions. These unhealthy interactions, in turn, place the child at increased risk for developing clinically concerning emotional and behavioral problems. Parental control has been implicated as a noteworthy transdiagnostic parenting behavior for both internalizing and externalizing disorders.[22] Parental control is oftentimes subdivided into behavioral and psychological control. Behavioral control is typically viewed favorably and involves a parent setting appropriate limits, implementing effective discipline techniques, and providing adequate supervision. Psychological control frequently has negative connotations and involves parenting practices that are overly controlling, such as constraining verbal expression or discouraging independent problem solving, thereby reducing a child's ability to develop a sense of autonomy and independence.[23] Appropriate behavioral control is typically viewed as a protective factor against pediatric behavioral health concerns, whereas high levels of psychological control have been shown to negatively impact the development and maintenance of both internalizing and externalizing disorders.[24]

Parents also influence their child's emotional and behavioral difficulties by modeling ineffective behaviors and coping strategies (eg experiential avoidance, emotional dysregulation, information processing biases), which are then imitated by their child.[25] Parents may perpetuate their child's emotional and behavioral difficulties by providing reinforcement for these behaviors. For example, research has shown that a child's information processing biases are reinforced through discussions with parents, wherein anxious children are supported in selecting avoidant solutions and aggressive children are encouraged to use aggressive solutions.[26]

Sleep Regulation

Among adults, sleep dysregulation is known to be comorbid with a broad range of psychiatric disorders.[27] Though less studied in children and adolescents, sleep disturbance is common among this younger population.[28] Furthermore, childhood sleep dysregulation is associated with a range of psychopathology, including disruptive behavior,[29] anxiety,[30] and depressive symptoms.[31] Harvey et al argue that sleep disturbance is not only *descriptively transdiagnostic* (ie, commonly co-occurring across various psychiatric disorders) but also *mechanistically transdiagnostic*. That is, Harvey and colleagues posit that sleep disturbance and psychopathology are etiologically linked. They provide a review of possible neurobiological pathways that may explain this link, including the association between circadian genes and psychopathology, the bidirectional relationship between sleep disturbance and emotion dysregulation, and the relationship between circadian systems and dopaminergic/serotonergic functioning. The group outlines clinical implications of the transdiagnostic nature of sleep and proposes a modular treatment for sleep disturbance in adults, which could be adapted for use with children and adolescents.[15]

Emotion Regulation

Emotion regulation has been described as the manner in which an individual modifies either internal emotional experiences or external emotional stimuli. According to Gross, "emotion regulation refers to the processes by which we influence which emotions we have, when we have them, and how we experience and express them."[32] More recent definitions have included increasingly nuanced consideration of the separate skills, processes, physiological indicators, and neural underpinnings that comprise emotion regulation.[33] Despite lack of consensus regarding its definition, emotion regulation is consistently identified as

a pertinent factor in a wide range of pediatric behavioral health concerns.[34]

The role of emotion regulation deficits in the development of both internalizing and externalizing disorders has led to its consideration as a transdiagnostic mechanism.[22,34] More accurately, emotion regulation components and strategies may be considered as a set of transdiagnostic mechanisms, including both automatic reactions (temperament, impulsivity, negative emotionality) and more voluntary or effortful strategies (eg, executive functioning strategies such as attentional control, inhibition).[35] Increasingly, focus has turned to the physiological measurement of emotional arousal, including functional imaging studies and measurement of cardiac vagal regulation.[36,37] These studies should provide additional information about the transdiagnostic role of emotion regulation.

Information Processing Biases

Information processing is described as the cognitive processes that influence an individual's behavioral response to a given stimulus.[38] Biases in information processing (eg, attention, appraisal, negative thinking) contribute to a variety of clinical presentations, including mood disorders, anxiety, disruptive behavior, and posttraumatic distress.[39] The distinction between emotion regulation and information processing is not well delineated, and several processes (eg, rumination, attention biases) are described under both umbrella literatures. For the purpose of this paper, information processing includes the sequence of cognitive processes that impact an individual's response to the environment, with a particular focus on rumination, appraisal, and attention bias.

Rumination, appraisal, and attention bias have all been identified as cognitive processes that underlie the development of both internalizing and externalizing psychopathology among children and adolescents. *Rumination* is defined as the passive and repetitive analysis of negative symptoms with the absence of active problem solving. It has been described as a mechanistic link between depression and anxiety and as a transdiagnostic factor across numerous disorders including emotional disorders, substance abuse, and eating disorders.[40] Furthermore, rumination has been found to play a role in the transition between internalizing problems and aggressive behavior among young adolescent males,[34] suggesting its value as a transdiagnostic mechanism that spans seemingly distinct areas of psychopathology. Similarly, biases of *appraisal*, or interpretation, play a role in multiple internalizing and externalizing behavioral health disorders.[22] These biases in the interpretation of external information include misinterpretation of social cues and cognitive errors such as catastrophizing and personalizing.[41] Appraisal biases have been identified among children demonstrating symptoms of depression, anxiety, and aggression.[42] Finally, the presence of attentional bias across both externalizing and internalizing disorders suggests its role as a transdiagnostic mechanism.[14] Fraire and Ollendick reviewed the literature on attentional biases in children with comorbid anxiety and oppositional disorders and identified biases towards threatening information (eg, angry faces), as well as negative information in general (eg, preferential recall of negative words).[22] Racer and Dishion presented preliminary evidence regarding the relationship between basic attention processes (alerting and orienting) and both internalizing and externalizing symptoms.[14] They highlighted the need for better measurement of attention processes and proposed attention training as a potentially effective transdiagnostic treatment.

Experiential Avoidance

Avoidance has been described as an occurrence in which "an individual does not enter, or prematurely leaves, a fear-evoking or distressing situation."[43] Chu and colleagues provide a detailed explanation of the role of avoidance as a transdiagnostic factor across depression, anxiety, and conduct problems (eg, oppositional defiant disorder, conduct disorder, and attention-deficit/hyperactivity disorder). The authors explain that the terminology used to describe avoidance differs across disorders, with avoidance acting as the underlying function of other processes, including escape from task demands, rumination, social withdrawal, and callous-unemotional responding. They propose the need for continued investigation in order to understand the transdiagnostic role that avoidance plays across disparate disorders.

Avoidance as an independent process has perhaps been most thoroughly explored by the developers of Acceptance and Commitment Therapy (ACT) and other third-wave cognitive and behavioral interventions (eg, Dialectical Behavior Therapy, mindfulness-

based approaches).[44] *Experiential avoidance* is defined as the tendency to escape or avoid unpleasant psychological processes such as thoughts, emotions, or sensations by attempting to change the form and frequency of these experiences.[45] The process is a central component of Hayes and colleagues' Functional Dimensional approach to diagnosis and treatment, which parallels the transdiagnostic movement in its emphasis on functioning rather than syndromal/diagnostic categorization. Research has demonstrated that experiential avoidance plays a role in adult depression, anxiety, substance abuse, posttraumatic stress disorder, and self-harm.[46]

Experiential avoidance has not been as widely studied among youth. However, there is evidence for the effectiveness of ACT, which targets experiential avoidance, in treating child and adolescent psychopathology. ACT has demonstrated success in treating children and adolescents with eating disorders, anxiety disorders, and chronic pain, as well as in improving parental coping and parenting practices.[47] Furthermore, experiential avoidance is widely understood to underlie various childhood internalizing and externalizing disorders and thus warrants attention as a transdiagnostic mechanism in pediatric behavioral health.[48]

Transdiagnostic Intervention Programs

Rapid growth has occurred in the number of theoretical and empirical papers describing transdiagnostic approaches to behavioral health. A Google Scholar search for the terms "transdiagnostic intervention psychology" during all years before 2010 produced 670 results; a search for the same terms in articles published between 2010 and mid-2015 produced 4,200 results. Despite this rapid growth in the use of the term *transdiagnostic*, variability exists with regard to how this term is applied. A majority of publications on the topic of transdiagnostic intervention use the term to describe interventions designed to treat 2 highly comorbid internalizing disorders (eg, depression and anxiety),[49] or multiple similar disorders such as anxiety disorders[50] or eating disorders.[51] The most promising existent transdiagnostic treatments focus only on comorbid anxiety and depression, resulting in a failure to address the high comorbidities between internalizing and externalizing disorders.

The Unified Protocols

As with many areas of psychotherapy research, early models of transdiagnostic intervention originated in the adult therapy literature.[49] The most studied and cited program is Barlow and colleagues' Unified Protocol for the treatment of Emotional Disorders (UP), which treats adult anxiety and mood disorders concurrently using traditional cognitive behavioral therapy (CBT) principles (eg, prevention of avoidance, behavioral exposure, cognitive restructuring), while also emphasizing emotional processes (eg, emotion awareness, regulation, emotional avoidance).[52] The UP has demonstrated efficacy in reducing symptoms of depression and anxiety in adults with a principal anxiety disorder.[53] Several child and adolescent-focused interventions have followed Barlow and colleagues' lead in treating comorbid anxiety and depression. These include the Unified Protocols for the Treatment of Emotional Disorders in Children & Adolescents (UP-C, UP-A),[54] which are downward extensions of Barlow's UP.

The UP-A was modified from the adult UP to treat anxiety and mood disorders in adolescents ages 12-17 years. Like the adult UP, the UP-A targets emotion regulation as a core feature of behavioral health and utilizes CBT-based treatment skills (eg, emotion awareness, cognitive reappraisal, preventing avoidance, and emotion exposures). The original adult UP was modified to be more developmentally appropriate by reducing the amount of jargon, increasing time for rapport and motivation building, increasing frequency of experiential exercises, and adapting the program to include parents.[54] The program has demonstrated efficacy in the concurrent reduction of both anxiety and depressive symptoms in a sample of 59 adolescents presenting with high rates of comorbidity and a principal diagnosis of either anxiety or depression.[55]

A further downward extension of the UP-A, the Unified Protocol for Children: Emotion Detectives (UP-C:ED), was developed to treat anxiety and/or depressive symptoms in children ages 7-12.[56] The UP-C:ED is a group-based treatment that utilizes developmentally-appropriate modifications (eg, reinforcement through rewards, increased parental involvement) to teach the core concepts and skills that are shared by the other versions of the UP (eg, emotion awareness, cognitive reappraisal, emotion exposures).[54] Prelimi-

nary open trial research suggests that the UP-C:ED may prevent child-reported anxiety symptoms in non-clinical populations[57] and reduce anxiety and depression symptoms in children with a principal anxiety disorder.[58]

The Unified Protocols represent progress in a movement towards effective behavioral health interventions that do not focus on distinct diagnostic categories. In order to meet the varied needs of children who present to behavioral health clinics, however, the scope of transdiagnostic interventions will need to include a broader range of clinical presentations. To date, the majority of transdiagnostic intervention programs focus exclusively on comorbid depression and anxiety. Given that childhood behavior problems represent the most common reason for referral to pediatric mental health services,[59] a comprehensive transdiagnostic approach to pediatric behavioral health will need to be applicable across a broad range of presenting concerns including both internalizing and externalizing presentations. Inclusion of seemingly disparate clinical presentations within the same intervention program is justified by the existence of shared mechanisms (eg, avoidance, sleep disturbance, emotional regulation), which were described earlier. Such broad applicability will require the development of additional assessment and treatment approaches that focus on underlying mechanisms of psychopathology, rather than on symptoms and diagnoses.

The MATCH-ADTC

The Modular Approach to Therapy for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH-ADTC) is distinct from interventions such as the Unified Protocol in that it extends focus with components designed to support the treatment of a broader range of problems, adding disruptive behaviors and traumatic stress to the Unified Protocol's focus on anxiety and depression.[60] The treatment consists of 33 freestanding modules drawn from cognitive behavioral therapy and behavioral parent training, to be used in the treatment of youth ages 7 to 15 years. The modules are selected and applied in an individualized combination and sequence, depending on the presenting concerns and treatment progress of a particular child or adolescent. Treatment modules, which include titles such as Problem Solving, Active Ignoring, Fear Ladder, and Learning to Relax, are selected according to decision flowcharts. In a randomized trial of 174 youths with clinically elevated anxiety, depression, and/or disruptive conduct symptoms, MATCH-ADTC was compared to standard manualized treatment (cognitive behavior therapy or behavioral parent training) and usual care. The program outperformed both control groups in symptom improvement trajectories over the course of treatment. Further, youths in the MATCH-ADTC groups had significantly fewer diagnoses post-treatment (mean of 1.23 diagnoses) than did youths who received usual care (mean of 1.86 diagnoses), with no significant difference in number of diagnoses at treatment outset.[61]

The MATCH-ADTC is in many ways consistent with a vision of comprehensive transdiagnostic pediatric behavioral health treatment. It is flexible, modularized, and designed to address both internalizing and externalizing concerns. However, although the MATCH-ADTC is transdiagnostic in the sense that it is designed to treat children with varied diagnostic presentations, treatment planning within the model remains dependent on symptom-focused diagnostic categories (ie, Depression, Traumatic Stress, Anxiety, Conduct Problems). Furthermore, initial evaluation of the program has focused on reduction of symptoms and diagnoses, without examining transdiagnostic mechanisms.[62] Although the MATCH-ADTC represents significant progress in the area of modular treatment approaches, it was not developed or marketed as a transdiagnostic intervention program, and it does not include the explicit focus on transdiagnostic mechanisms that would characterize a comprehensive transdiagnostic approach to assessment and intervention.

That being said, the MATCH-ADTC represents an important movement towards utilization of the common elements across EBTs and development of modular treatments that can flexibly target individualized needs. Rather than continuing to develop and validate new, stand-alone, manualized treatments, this new approach draws upon existent intervention research. As Chorpita and colleagues note, "continued proliferation of knowledge about treatment will not help unless we get much, much better at summarizing, synthesizing, integrating, and delivering what we already have."[63] Using a distillation and mapping model (DMM), Chorpita and Daleiden defined 41 treatment components (eg, communication skills, exposure, relaxation, behavioral contracting, time out) that are

common across varied EBTs.[64] To bridge the gap between "common elements" approaches (eg, MATCH-ADTC) and transdiagnostic approaches, additional research is needed to clarify whether common elements treatment components target and effectively treat specific transdiagnostic mechanisms. For example, it seems likely that the common treatment element *relaxation* positively impacts the transdiagnostic mechanism *emotion regulation*, which likely leads to a reduction in symptoms. Research is needed, however, to identify and define such relationships among common treatment elements, underlying mechanisms, and behavioral health.

Transdiagnostic Assessment

A central impediment to the further advancement of transdiagnostic research and intervention is the categorical and symptom-focused nature of existent assessment tools and methodology. Given the relative dearth of mechanism-focused measurement tools, purportedly transdiagnostic interventions typically continue to base treatment planning on the assessment of symptoms and diagnostic labels (eg, *anxiety*), rather than on an assessment of underlying mechanisms (eg, sleep disturbance, parenting practices). It is expected that this trend will continue, in large part due to payors' requirements related to the use of diagnostic categories, as well as professional attachment to these terms. Transdiagnostic theorists aim to shift focus away from symptoms and diagnostic labels and towards the driving mechanistic factors that more accurately explain pediatric behavioral health problems. Although many skilled clinicians already attend to the role of mechanisms in their clinical formulations, the lack of validated mechanistic assessment tools limits the extent to which clinicians and researchers can explicitly and objectively measure these mechanistic processes. Because mechanisms are not regularly measured, the causal link between mechanisms and clinical presentation remains, to a certain degree, theoretical. Much research is needed in order to both (1) develop reliable, valid tools with which to measure mechanistic processes, and (2) more clearly establish the relationships between underlying mechanisms and clinical presentations.

Several measures have demonstrated utility in assessing the specific transdiagnostic mechanisms described earlier (eg, parenting, sleep regulation, emotion regulation, information processing biases, and avoidance). These include, among others, the Alabama Parenting Questionnaire,[65] the Parental Acceptance and Action Questionnaire,[66] the Pediatric Sleep Questionnaire,[67] the Difficulties in Emotion Regulation Scale,[68] the Children's Automatic Thought Scale (CATS),[69] the Response to Stress Questionnaire,[70] the Avoidance and Fusion Questionnaire,[71] the Emotion Regulation Questionnaire,[72] and The Parenting Scale.[73]

Although the majority of these measures were not explicitly developed for the purpose of measuring mechanisms, their potential as transdiagnostic measures warrants further attention and study. However, given that these measures typically assess the presence of individual mechanisms, clinicians must use several measures in order to evaluate numerous mechanisms, which can become costly and time prohibitive. Thus, development and validation of a unified assessment instrument aimed at simultaneously measuring the presence of multiple core mechanisms is needed.

PMHI Transdiagnostic Pilot Projects

The transdiagnostic workgroup of the Pediatric Mental Health Institute (PMHI) at Children's Hospital Colorado/University of Colorado School of Medicine was originally tasked with designing a transdiagnostic assessment and intervention program to address the complex needs of patients presenting to the PMHI's behavioral health programs. The workgroup began by delineating a comprehensive, collaborative, transdiagnostic assessment and intervention program. As shown in Figure 1, a patient in such a program would begin with a comprehensive assessment aimed at identifying the presenting concern, as well as relevant underlying mechanisms.

However, during the initial stages of the program development process, it became apparent that the lack of validated tools with which to measure mechanisms represented a significant barrier to the advancement of such a transdiagnostic program.

Without a better understanding and identification of common mechanisms that underlie clinical presentations, newly-developed transdiagnostic intervention approaches may not be clearly distinguishable from or improve upon previously-developed and poorly-disseminated EBTs. In response to this limitation, the PMHI transdiagnostic workgroup has undertaken a

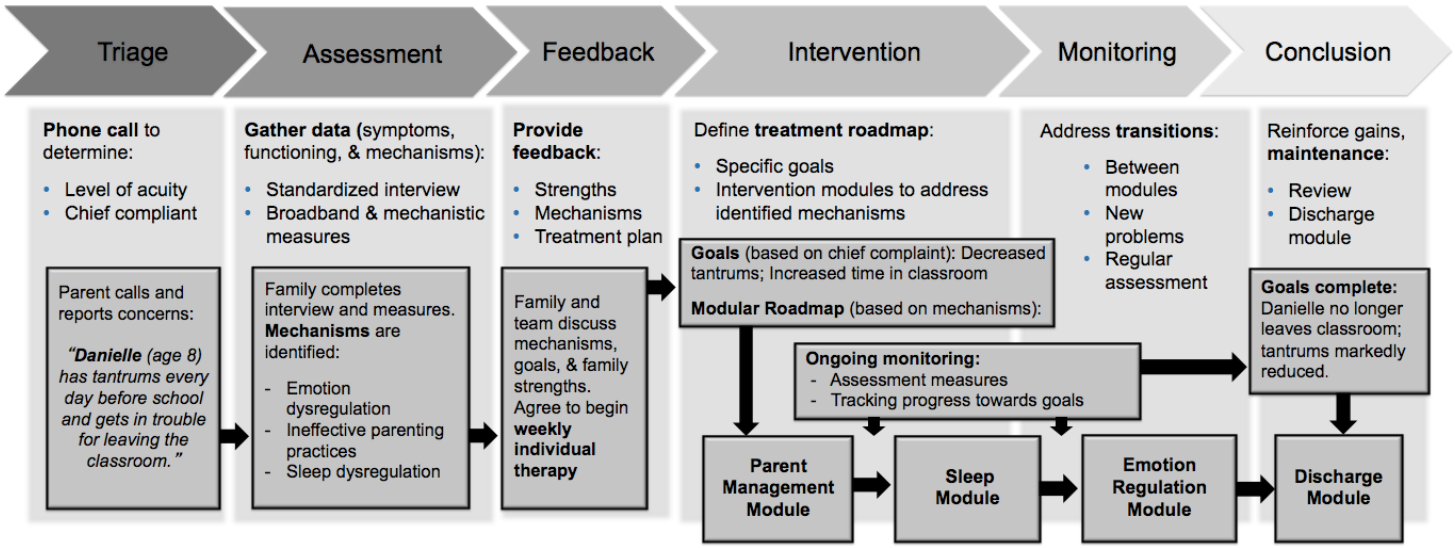

Figure 1. Overview of a proposed transdiagnostic assessment and intervention program, with hypothetical patient experience

series of pilot projects aimed at addressing the measurement gap in the transdiagnostic literature. These projects have differentiated themselves from existent transdiagnostic research by prioritizing the measurement of mechanisms over the measurement of symptoms or diagnoses. Specifically, the PMHI transdiagnostic workgroup projects have focused on the development and implementation of a transdiagnostic semi-structured clinical interview and the creation of written parent and child unified measures of core transdiagnostic mechanisms. Both projects discussed below received approval from the Organizational Research Risk and Quality Improvement Review Panel at Children's Hospital Colorado.

Transdiagnostic Interview

First, the transdiagnostic workgroup has begun to evaluate the feasibility and utility of a new transdiagnostic semi-structured interview, which is currently in its second iteration. This interview retains traditional intake questions designed to identify symptoms and evaluate the presence of any psychiatric diagnoses, while also evaluating the presence of pertinent underlying mechanisms. At the beginning of the intake appointment, patients and caregivers are asked to identify the 3 problems of greatest concern to them and to rate the severity of those problems on a scale ranging from 0 (not at all) to 10 (very much). This consumer-guided "top problems" assessment approach was developed by Weisz and colleagues[74] in an effort to support clinicians in efficiently and systematically using evidence-informed treatment planning and progress monitoring tools. Furthermore, the top problems approach has been proposed as a method that can support the study of empirically-derived constructs, such as transdiagnostic mechanisms, while also providing family-centered care and maintaining psychometric integrity. Following the identification of top problems, PMHI pilot clinicians support families in evaluating the presence and impact of different mechanisms on the top 3 identified problems.

During the first iteration of the interview, mechanisms were assessed through a series of targeted questions, which were largely informed by behavioral theory and the literature on functional assessment. An operational definition of how these mechanisms translated into behaviors, information regarding the antecedents and consequences associated with different mechanisms, and strategies employed to manage these mechanisms were obtained. See Table 1 for an example of pertinent questions included in this first iteration of the PMHI's transdiagnostic clinical interview. Approximately 22 transdiagnostic interviews were completed in the initial phase of this project. Clinicians reported moderate satisfaction (1=Strongly disagree to 6=Strongly agree; M=3.88) with the new transdiagnostic intake process and identified the following mechanisms as most beneficial for assessment and diagnosis: emotion regulation (M=4.87), parenting (M=4.81), and experiential avoidance (M=4.64). Clinicians' qualitative responses indicated the transdiagnostic intake process yielded critical information for case conceptualization, differential diagnosis, and treatment planning. However, responses also

revealed concerns regarding the length of the transdiagnostic interview, which lasted up to 120 minutes in duration.

Based upon clinician feedback, modifications are currently underway to address concerns regarding the feasibility of the transdiagnostic interview and to continue to enhance its utility in identifying mechanisms and informing treatment planning. The transdiagnostic workgroup is building upon the PMHI outpatient clinic's current intake process, expanding the original 90-minute intake interview to 2, 60-minute sessions. During the first visit, families will participate in a traditional diagnostic interview and complete a written measure of transdiagnostic mechanisms, which is described in the next section. At the end of this first visit, the clinician will support families in identifying a target top problem, as previousy described. For 1 week, families will use a home-based worksheet aimed at tracking the situations, thoughts, feelings, behaviors, and outcomes associated with this top problem. During the second visit, families will engage in a revised semi-structured clinical interview informed by functional assessment and behavior-chain analysis principles in order to gather information regarding underlying mechanisms and functional impairments. At the conclusion of the second visit, clinicians and families will discuss evaluation findings, engage in psychoeducation regarding the transdiagnostic approach to treatment, and collaboratively develop a treatment plan that addresses mechanisms and emphasizes both the reduction of impairment and the promotion of wellness.

Transdiagnostic Measures

In a related pilot project, the PMHI transdiagnostic workgroup is currently working to develop and validate 2 transdiagnostic measures, a 62-item Parent Transdiagnostic Mechanism Questionnaire (PTMQ) and a 39-item Child Transdiagnostic Mechanism Questionnaire (CTMQ). These measures aim to evaluate the presence of multiple core mechanisms simultaneously, as no currently-validated measures are available to accomplish this goal. Item development was guided by relevant theories underlying a transdiagnostic approach to pediatric mental health. Specific items were generated based on a review of the empirical literature of pertinent mechanisms, as outlined above. Items with high factor loadings on previously-validated measures were referenced to inform the development of specific items on each measure. See Table 2 for a summary of items referenced from other measures, as well as their associated factor loadings based upon previously-conducted studies examining the psychometric properties of these items. These measures have been incorporated into the PMHI transdiagnostic assessment process (described in the previous section), as they provide helpful supplemental information about underlying mechanisms and functional impairment. Currently, the measures are being completed during the first session of the 2-step intake process by all caregivers and by all patients ages 8 and older. These newly-developed transdiagnostic measures have been completed by a small subset of patients and caregivers both to evaluate the readability of the items developed and to assess the feasibility of completing these measures during an intake appointment. Preliminary data have demonstrated good understanding of the items on both the child and parent measures, and completing these measures during the intake appointment has been shown to be feasible. Future studies aimed at examining the psychometric characteristics of this measure with a larger sample, identifying clinical cut-off scores, clarifying the relationship between the presence of underlying mechanisms and emotional-behavioral problems, and evaluating the proposed 5-factor model for these instruments using confirmatory factor analysis will be needed.

Conclusion

As translational mental health research turns its attention from symptoms and diagnoses to transdiagnostic mechanisms, clinical programs have the opportunity to develop and use new tools and findings to reshape clinical interventions and better address the complex behavioral health needs of pediatric patients. In keeping with the aims of RDoC, closer examination of transdiagnostic mechanisms such as those described in this paper (eg, parenting, sleep regulation, emotion regulation, information processing biases, and experiential avoidance) will provide vital information about the etiology and maintenance of child and adolescent behavioral health problems. More work is needed to expand pediatric transdiagnostic treatments to include externalizing as well as internalizing symptoms, to push beyond traditional models of in-

tervention development and dissemination (ie, manualization), and to develop effective assessment tools for identifying pertinent transdiagnostic mechanisms. With continued research and practical application, the burgeoning transdiagnostic movement has the potential to transform the way in which behavioral health disorders are conceptualized and treated.

Table 1. Excerpt from original transdiagnostic interview, including top problems and mechanism-focused questions.

PROBLEM LIST (0=Not at all; 10=Very much)	
Top 3 Problems **(per caregiver)**: Problem 1: Problem 2: Problem 3:	Top 3 Problems **(per child/adolescent)**: Problem 1: Problem 2: Problem 3:
MECHANISM (eg, experiential avoidance)	
Patient avoids/struggles to tolerate which of the following: bodily sensations, memories, thoughts, emotions, situations, etc. Examples of avoidance: Frequency:___ times per {day, week, month, year} for ___ {length of time}.	
Avoidance most likely: When: Where: With: While:	**Avoidance least likely:** When: Where: With: While:
Antecedents/triggers of avoidance: Consequences (punishment or reinforcement) of avoidance: Avoidance usually stops when: Strategies to address avoidance: Strategies impacted avoidance?	Avoidance impacts {Problem 1} by: Avoidance impacts {Problem 2} by: Avoidance impacts {Problem 3} by:

Table 2. Factor loadings and rating scales associated with development of items for CTMQ/PTMQ

Note: Factor loadings are based upon previously conducted studies examining the psychometric properties of these items.

Rating Scale(s)	Factor Loading	Item
Emotion Regulation		
Difficulties in Emotion Regulation Scale[68]	.79	I cannot pay attention to anything else.
Difficulties in Emotion Regulation Scale	.85	I can't control what I say or do.
Difficulties in Emotion Regulation Scale	.88	I have trouble understanding how I am feeling.
Emotion Regulation Questionnaire[72]	.66	I try to hide my feelings or keep my feelings to myself.
Information Processing		
Response to Stress Questionnaire[70]	.72	I deal with my problems by wishing they would go away.
Emotion Regulation Questionnaire	.76	When I want to feel better about something, I change the way I'm thinking about it.
Children's Automatic Thought Scale[69]	.80	I think, "I am worthless."
Children's Automatic Thought Scale	.83	I think, "Most people are against me."
Experiential Avoidance		
Response to Stress Questionnaire	.81	I deal with a problem by pretending it has not really happened.
Response to Stress Questionnaire	.79	I engage in other activities (eg eat, sleep, play video games) to distract myself from feeling upset.
Avoidance and Fusion Questionnaire[71]	.59	I push away thoughts and feelings I don't like.
Parenting Practices		
Alabama Parenting Questionnaire[65]	.68	I provide rewards or give something extra when my child is behaving well.
The Parenting Scale[73]	.74	If my child gets upset when I say "no," I back down and give into my child.
Parental Acceptance and Action Questionnaire[66]	.59	I try hard to avoid having my child feel sad, worried, or angry.
Sleep Regulation		
Pediatric Sleep Questionnaire[67]	.89	How would you rate your child's sleep quality overall?

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Infant and Preschool Adaptations of Inhibitory Adult Tasks Associated with Psychiatric Illness

*Elizabeth Calvin, MD; Amanda Hutchinson, MD; Randal G. Ross, MD**

Abstract

Many psychiatric diseases are often conceptualized as neurodevelopmental, where the onset of clinically diagnosable illness is the end result of a years-long, or even decades-long, alteration in brain development. The aberrant brain development can originate as early as the pre- or early post-natal period; thus, efforts aimed at understanding and preventing disease onset are going to require methodologies appropriate for use in young children and infants. One approach to develop early developmental methodologies is to take methods used in the study of adults and modify them for infant or preschool use. This review explores the potential for use, in infant and preschool populations, of 4 commonly-employed tasks of cognitive inhibition in adults: the antisaccade task, prepulse inhibition, P50 sensory gating, and smooth pursuit eye movements. Only P50 sensory gating has received much attention as a marker of early vulnerability to later onset of psychiatric illness; however, infant variants of these methodologies are also available for the antisaccade task and smooth pursuit eye movements. By utilizing adaptations of traditional adult tasks, research focused on the earliest phases of development is feasible and has the potential to improve primary prevention of psychiatric illness.

Background

Psychiatric disease is often conceptualized as a neurodevelopmental result of a decades-long interplay between genetic and environmental factors. Most modern versions of this Neurodevelopmental Hypothesis[1,2] propose 2 particularly critical periods of brain development: a perinatal period where vulnerability is established and a later childhood, adolescent, or early adult period where vulnerability becomes symptomatology. Brain changes that occur during the perinatal period are not deterministic in that the majority of children at risk will never develop a chronic psychiatric disorder. In a similar fashion, genetic and environmental factors that influence the adolescent or young adult emergence of psychiatric symptoms are far less strongly associated with increased risk in non-vulnerable individuals.

Comprehensive prevention strategies need to include evaluation and intervention at much younger ages: during pregnancy, infancy, and preschool years. To this effect, the National Institute of Mental Health has called for an increase in research focusing on the developmental aspects of psychiatric disease as 1 of 4 main strategic objectives (Strategic Objective #2, NIMH).[3] There have been increasing questions surrounding how to approach the study of psychopathology in general. Many psychiatric symptoms appear clinically similar across a wide range of diagnoses. For example, active psychosis in someone who has a diagnosis of bipolar disorder may be clinically indistinguishable from that in someone who has schizophrenia or schizoaffective disorder. Additionally, some individuals with the same diagnosis may have a large variation in symptomatic presentation. Supporting the symptomatic overlap frequently seen in clinical presentations, research has thus far been unable to associate current specific diagnoses with quantifiable biomarkers or genetic locales. Again using psychosis as an example, despite a significant effort to identify specific genetic markers,

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currently identified genetic variants appear to confer similar risk across multiple disorders.[4] Thus, the NIMH has also called for the development of a new way of classifying psychiatric disease based on neurobiological measures and observable behavior (Strategy 1.4).[3] To this end, basic domains of functioning are being studied across multiple diagnoses and along multiple levels. These diagnostic and developmental dilemmas are present globally in psychiatry; however, to illustrate, we will utilize one facet of functioning, cognitive inhibition, as a microcosm of possible translation and future research.

In adults, there are several tasks that have been developed to study cognitive inhibition. Performance deficits in these tasks have emerged as potential endophenotypes, or characteristics of genes that predispose an individual to disease.[5] These include (but are not limited to) P50 sensory gating, inhibition of pro-saccades during an antisaccade task, smooth pursuit eye movement aberration, and pre-pulse inhibition. These tasks could prove ideal for studying developmental trajectories and early symptomatology. However, in children of certain ages, limited developmental capacity and the difficulty faced in communicating research procedures make utilization of these tasks difficult to impossible; simpler tasks must be used. In recent years, recognition of these differences and the desire to examine development has spawned multiple infant and preschool adaptations of adult inhibitory tasks. This manuscript reviews infant and preschool versions of adult measures of cognitive inhibition, highlights what has been shown through them thus far, and examines potential future areas of research. We plan to illustrate that tasks have been associated with risk of later disease onset, have developmentally appropriate correlates, and are usable in preschoolers and infants.

Method

We used “eye movements,” “saccade,” “sensory gating,” “P50,” “prepulse inhibition,” and “smooth pursuit” as independent search words to identify full texts in the OVID and PsychInfo databases before July 2014. Each search was limited to studies of “all children (ages 0-18 years).“ The reference lists of each article were further examined to include studies not listed in above databases. A more limited search was completed for the same key words for adult populations.

Antisaccade

Rapid eye movements, which direct gaze to a specific location in visual space, are termed “saccades.” The antisaccade task is an occulomotor paradigm wherein the participant watches the presentation of a visual cue, and then is instructed to move his eyes to the mirror image of that cue while his eye movements are recorded (Figure 1). Cognitive inhibition is tested in that one must inhibit the more biologically-programmed, or prepotent, response of looking at a new visual cue, and instead follow the examiner’s instructions to look at the empty visual space at its mirror image.

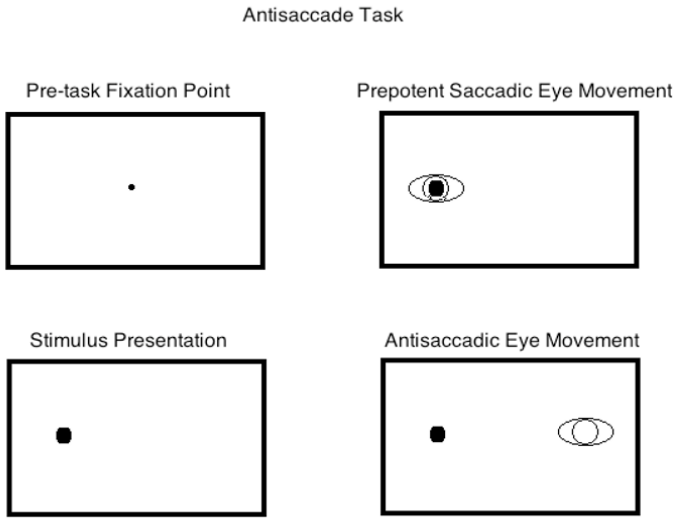

Figure 1. Example of antisaccade task. The participant looks at a fixation point (upper left), which is replaced by a stimulus (lower left). The participant is asked to inhibit the prepotent response of looking at the stimulus (upper right), and instead looks to the mirror image of that stimulus (lower right).

Adult Literature

This task has been used extensively to study disordered psychiatric populations in adults. Despite typical performance on saccadic movements to a target, schizophrenia patients have consistently been found to have an increased error-rate on the antisaccade task, moving their eyes to the presented visual cue instead of inhibiting that response and looking toward its mirror image.[6-10] Patients with other psychotic illnesses, including bipolar disorder and major depressive disorder with psychotic features, have also been

found to exhibit an increased error rate, particularly during initial psychotic episodes,[11,12] though some studies have failed to show increased antisaccade error rates in those with bipolar disorder.[13,14] Many studies have also found an increased latency, or decreased speed of response, in correct antisaccades in schizophrenia,[8,9,12,13,15] further suggesting increased difficulty of this task for those with psychosis.

The initial Consortium on the Genetics of Schizophrenia analyses found antisaccade deficits to be significantly heritable with a heritability estimate of 42%.[16] Similarly, unaffected first-degree relatives of psychotic probands with antisaccadic abnormalities also have poorer performance on the antisaccade task.[6,17,18] Thus, the antisaccade task appears to be a marker of risk at least for schizophrenia.

Child/Adolescent Literature

In children and adolescents, developmental differences in the antisaccade task must be considered. The younger the child, the more slowly and inaccurately the task is performed. Adult performance in latency is not achieved until early adolescence and accuracy continues to improve into early adulthood.[19-22] Despite these developmentally-limited capacities, increased errors have still been visualized in children currently diagnosed with ADHD, autism spectrum disorders, reading disorders, obsessive compulsive disorder, anxiety, depression, psychosis, and bipolar disorder.[23-25] Similar to the adult literature, it has been estimated that greater than half of the variance in performance in children is due to genetic influences.[26]

Preschool/Infant Adaptations

Giving verbal instructions to a preschooler or an infant is problematic to impossible given varying abilities in receptive language. Additionally, adult methodology typically calls for head restriction (usually with a bite bar or chin rest), but infants and preschoolers are less likely to tolerate head fixation. Further, infants control the direction of their gaze using coordinated head and eye movements,[27] so the head must be free to observe typically utilized gaze.

In studying antisaccades in infants or preschoolers, cognitive inhibition must still be tested. In other words, the infant must have the choice to look at a stimulus, but inhibit that response and look to the mirror image of that stimulus instead. In the infant antisaccade paradigm,[28,29] subjects are encouraged to make an eye movement away from the cue (an antisaccade) by making the second stimulus more attractive than the cue itself. Infants view a fixation, followed by simultaneous presentation of the fixation and the cue, and after a delay, a more attractive (more visually stimulating) target appears opposite the location of the cue. A decrease in saccades toward the cue is observed over time as infants learn that the cue predicts the appearance of an attractive stimulus at the contralateral location. Head movements have been examined by positioning a steel ball bearing on the infant's forehead, enabling recording of head position (along with eye position) utilizing infrared light (Figure 2). With these methodological changes, antisaccade responses occurred on an average of 25.9% of trials (8.3 out of 32) in infants aged 3 to 11 months as compared to saccades toward the initial cue, which occurred in 28.6% (9.2 out of 32) of trials in infants with no known perinatal complications. In other words, infants responded to 50% of presented trials, and of the trials they responded to, they performed antisaccades approximately 50% of the time.[27]

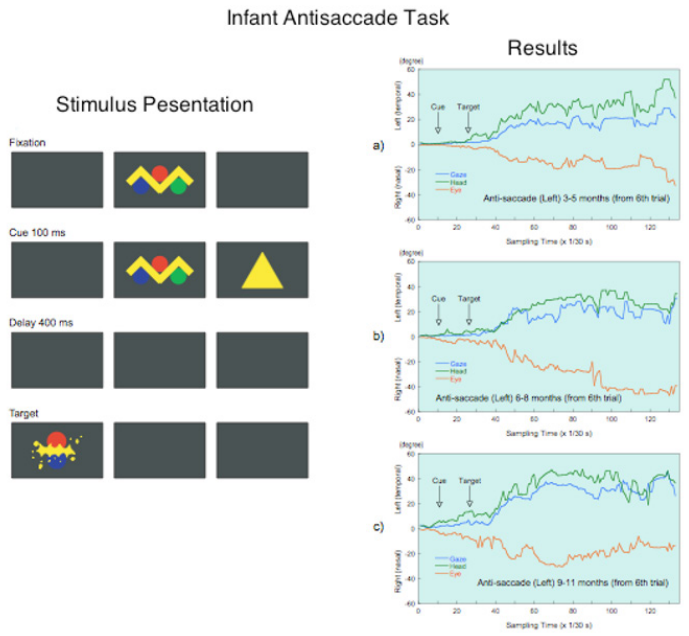

Figure 2. Example of an Infant Antisaccade Task. On the left, presentation of a fixation image is followed by stimulus (or cue) presentation, which is in turn followed by a delay and the presentation of a more attractive stimulus at the mirror image of original stimulus. As infants learn the stimulus precedes the presentation of a more attractive stimulus, they will complete an antisaccade to the location where they expect the more attractive stimulus to appear.

On the right, example tracings are shown. Gaze (blue line) is calculated utilizing eye (red) and head (green) positions. Examples of infants (1) 3-5 months, (2) 6-8 months, and (3) 9-11 months are shown. Adapted with permission.[27]

Preschoolers/Infants at Risk for Psychiatric Illness

No papers were found examining antisaccades in preschoolers or infants at higher risk of later psychiatric illness.

Summary

The antisaccade task is an effective research tool where performance, in adults, is heritable and associated with psychotic illness, and an adapted task has been used successfully in infants. No papers were found examining antisaccades in preschoolers or infants at higher risk of later chronic mental illness given genetic or environmental risk factors. Researchers may be hesitant to perform this task in younger populations given the likelihood of extremely high error rates and presumed lack of specificity in association with diagnosis given the high number of diagnoses associated with poor performance in childhood. However, the infant error rate of 50% is the same as children aged 5-8 in the typical antisaccade task.[22] In considering utilization of this task, it may be helpful for the subject to undergo more trials to facilitate a greater response percentage, particularly given that learned behavior is necessary to elicit an antisaccade to an anticipated more appealing target stimulus. Additionally, some caution must be taken when comparing the adult and infant results as the tasks have fundamentally different protocols, and eye movements themselves may be somewhat different in children and adults.[23]

Smooth Pursuit Eye Movements

While performing smooth pursuit eye movement tasks, the participant watches a monitor, which presents a moving visual target. The individual is instructed to keep his eyes directly on the target and follow movements as closely as possible while corresponding eye movements are recorded. Several necessary component abilities, such as prediction of target movement, maintenance of eye movement velocity, and cognitive inhibition can be studied by looking at specific portions of smooth pursuit. Cognitive inhibitory dysfunction can be seen when saccadic movements intrude, because to utilize smooth pursuit, the saccadic system must be inhibited. In other words, one can passively examine the participant's ability, or lack thereof, to inhibit saccades while utilizing smooth pursuit (Figure 3).

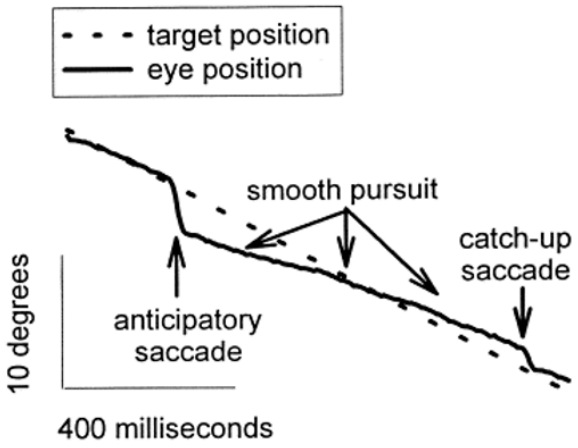

Figure 3. Sample tracing of smooth pursuit tracking from an individual with presumed genetic risk of schizophrenia (child of a parent with schizophrenia). The first arrow notes an anticipatory saccade where the subject's eyes jump ahead of the moving visual stimulus. The subject then utilizes smooth pursuit and makes a catch-up saccade when his eyes fall behind the target position. Adapted with permission.[30]

Adult Literature

Global detriments in smooth pursuit eye movement task performance was first observed in schizophrenic patients in the early 1900's.[31] It is now one of the most replicated deficits in the psychophysiological literature on schizophrenia.[7,32] Smooth pursuit abnormalities have been found in individuals with ultra-high clinical risk of developing psychosis,[33] schizotypic features,[34] bipolar symptoms and psychosis,[35] bipolar disorder,[36,37] acute mania,[38] and psychotic symptoms associated with PTSD.[39]

Biological relatives of patients with schizophrenia have also been shown to exhibit high rates of dysfunctional smooth pursuit eye movements,[15,30,40-42] and heritability has been estimated at between 40% and 60%.[43] Global measures of smooth pursuit eye movements appear to be relatively unaffected by most antipsychotic medication[44,45] or antidepressants, and there does not appear to be a significant correlation between acute psychopathology or duration of illness.[32,45-47] Atypical neuroleptics, such as clozapine or

other psychotropics, such as lithium, however, may adversely affect smooth pursuit.[48-50]

With the consistent finding that global eye tracking and smooth pursuit are impaired in schizophrenia patients and their relatives [32,41,51] as well as in other disorders such as autism,[52] depression,[53] Parkinsonism,[54] and ADHD;[23,55] additional research has sought to determine specifically which eye movement components are most likely endophenotypes. The heritability of generic saccades in smooth pursuit has been estimated at 66%, catch-up saccades (saccades occurring in the direction of target motion that move the eye from a position behind the target to a position near the target) at 61%, and anticipatory saccades (intrusive saccades occurring in the direction of target motion that move the eye from a position on or near the target to a position ahead of the target) at 62%.[43] A meta-analysis examining 18 component measures of eye movement dysfunction found that only anticipatory saccades (and not generic saccades that occur within smooth pursuit) were increased in relatives of those with schizophrenia.[51]

Additionally, several components of smooth pursuit eye movements, including anticipatory saccades, have been found only in schizophrenic patients and are absent in normal subjects or relatives of depressed patients.[56] A further subset of anticipatory saccades, leading anticipatory saccades (which are smaller in amplitude) are also both present in unaffected relatives of schizophrenic probands[57] and differentiate patients with schizophrenia from those with ADHD,[55] further supporting possible specificity to schizophrenia. Leading saccades also appear to be sensitive[58] with a large effect size,[32] specific,[55] and tied to genetic vulnerability.[30] However, it should be noted that not all studies have found differences in anticipatory saccade frequency[59] or indicated stability in this measure over time.[46]

Child/Adolescent Literature

Smooth pursuit tracking improves from the ages of 7-15,[60] and by late adolescence, smooth pursuit reaches adult levels of functioning,[61,62] with age expected to account for 20% of the variance.[60] However, some individual components of smooth pursuit may have different maturational rates. For example, leading saccades (small anticipatory saccades) may be mature by the age of 6, and an increase in frequency of leading saccades has differentiated children at risk of developing schizophrenia.[63]

Higher rates of smooth pursuit eye-tracking dysfunction (with some studies including abnormalities in catch-up and anticipatory saccades) have been seen in children with schizophrenia,[64,65] adolescents with a history of schizophrenia onset in childhood,[64,66] and in teenagers with psychosis not otherwise specified.[64] The proportion of total eye movement time spent in anticipatory saccades has also been shown to differentiate those who are more likely to carry genetic risk factors for schizophrenia,[30] children of a schizophrenic parent,[67] and in children who themselves have schizophrenic symptoms.[30] An increase in anticipatory saccades has also been seen in childhood onset schizophrenia patients relative to both normal controls and children with ADHD, indicating that the deficits seen in schizophrenia cannot be attributed to attention dysfunction alone.[66] Additionally, increased frequencies of leading saccades appear to be present in 94% of children with schizophrenia compared to only 19% of typically developing children.[63]

Poor performance has also been seen in parents and other first-degree relatives of those with childhood onset schizophrenia,[63,65,68] and in teenage children with a schizophrenic parent.[69]

Preschool/Infant Adaptation

Many studies have found smooth pursuit in early infancy,[70-72] even in the first few days of life,[73] with smooth pursuit consistently emerging by 4-8 weeks, and having significantly improved by 4-6 months of age.[71,74,75]

In older children and adults, this task traditionally requires head immobilization, such as with a chin rest and forehead strap. However, infants utilize both head and eye movements to initiate and continue smooth pursuit.[71] Head tracking also increases with age and has a large lag time, with the contribution of the head increasing over time in the first several months of life.[71] Different subjects may also utilize different proportions of head and eye movements in order to attempt to stabilize gaze.[76] Here also, eye tracking is simply harder to record given smaller facial dimensions.

Higher rates of variability are also found,[71,77,78] frequently leading to rejection of data far from the

mean, and greater fluctuations in attention may affect results.[64,77] Results may be affected by anxiety and fatigue,[78] which may be difficult to quantify or standardize.

The ability of an infant to track also depends on the size and speed of the target,[71] and younger infants spend less time in general utilizing smooth pursuit, with a 1-month-old typically being engaged in smooth pursuit approximately 40% of the time as compared to 90% in adults.[75] Smooth pursuit in infants is also affected by history of prenatal corticosteroids, gestational age, birth weight, bronchopulmonary dysplasia, retinopathy of prematurity, periventricular leukomalacia, and a history of intraventricular hemorrhage,[76,79] making screening and participant selection of utmost importance.

Opto-electronic devices have been developed with LEDs to record the head position of the infant and miniature electrodes to record electro-oculographic data from the outer canthi,[71,76] enabling dual quantification of gaze and smooth pursuit. However, optimal parameters regarding target size and speed for specific age ranges have yet to be elucidated.

Preschoolers/Infants at Risk for Psychiatric Illness

One report found that infants aged 6 months who were exposed to prenatal maternal anxiety, as compared to those without this risk, exhibited less percentage of time in smooth pursuit, with more frequent forward saccadic activity.[80] No other papers were found examining smooth pursuit in preschoolers or infants at higher risk of psychiatric illness.

Summary

Smooth Pursuit Eye Movement tasks appear ready for use in infants and preschoolers. In adults, dysfunction is reliably seen in those with psychosis, those at risk of psychosis, and in their biological relatives. This data has been confirmed in adolescents and children with psychosis as well. Component measures that may more clearly represent endophenotypes for schizophrenia and psychosis have also been found.

In infants, global smooth pursuit tracking measures have significantly improved only months after birth, and component measures may also mature prior to the entire tracking system, further increasing the possibility that studies in younger children are plausible.

When examining differences between those with psychosis or its risk and controls, some have argued that attention may mediate difference. However, while attention-enhancing maneuvers improve smooth pursuit of typical individuals and those with schizophrenia, it does not abolish the difference between them.[81,82] Additionally, some may be reluctant to conduct studies without optimal parameters regarding target size and speed for younger age ranges. If similar age ranges were utilized between the 2 comparison groups, however, these concerns could be accounted for.

Prepulse Inhibition

Prepulse Inhibition (PPI) is an auditory task wherein the participant lays supine in a reclined chair with his or her eyes open. A startle stimulus of broadband noise is presented after a prepulse stimulus of lower intensity; movements of the orbicularis oculi muscles are recorded. Cognitive inhibition is passively tested in that the presence of a prepulse causes inhibition of the participant's response to the startle stimulus as evidenced by a diminished response (Figure 4).

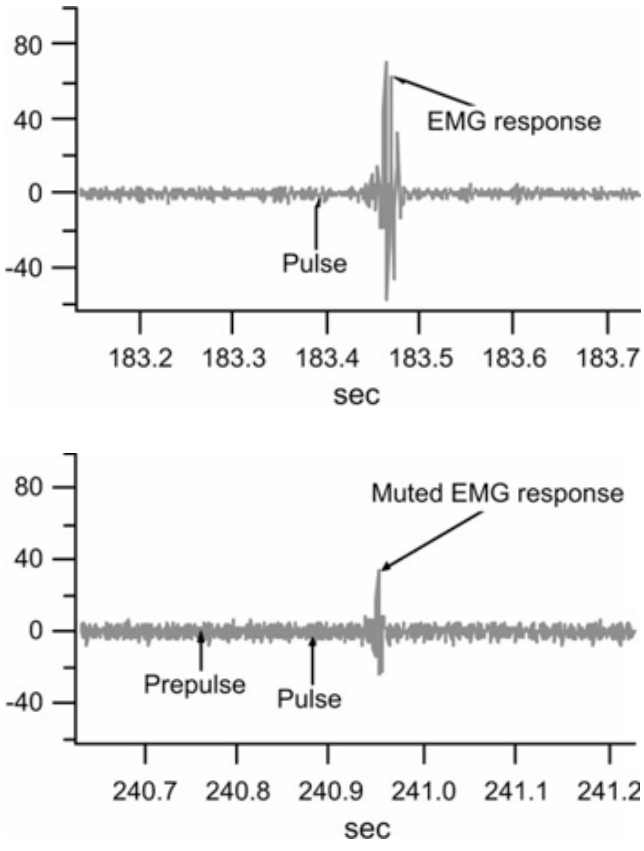

Figure 4. Example of Prepulse Inhibition (PPI). On the left, a typical response to an auditory stimulus is shown. On the right, Prepulse Inhibition, as evidenced by a diminished response, is achieved with the addition of a prepulse. Adapted with permission. [83]

Adult Literature

This task has been well described in adult populations with psychopathology. For example, although initial startle reactivity is the same[84] compared to those without a known psychiatric disease, those with schizophrenia continue to have a larger startle response, as measured by greater movement of the orbicularis oculi muscles, despite the presence of a prepulse.[85-88] This deficient PPI has been correlated with the positive and negative symptoms of schizophrenia[85] and has also been seen in those with schizotypal personality disorder,[89] as well as in some studies of those with bipolar disorder.[90] Deficits in PPI have been seen in individuals at risk for and currently experiencing their first episode of psychosis [84,91] and have also been noted in those with acute mania[92] as opposed to those with remission of bipolar symptomatology, where normal levels of PPI have also been described.[93]

First degree relatives of those with schizophrenia and bipolar disorder have been found to exhibit decreased PPI.[90,94,95] Heritability of PPI in those with schizophrenia has been estimated at 32%,[16] suggesting that PPI is also a marker of genetic vulnerability to disease.

It should be noted that the details of the task have been shown to have significant effects on results. For example, weaker prepulses (2 dB above the background), produce facilitation, or a larger startle response with the presentation of the stimulus,[85] and more intense prepulses typically produce a larger PPI effect.[85,96] Other subtle changes in the background noise, prepulse, and stimulus may also alter results.[85] Further, patient characteristics contribute to manifestations of PPI. Gender,[97-100] smoking status,[100,101] current symptomatology,[85] whether or not the individual is asked to attend to the stimulus,[102-104] and treatment with antipsychotics (which have been associated with improved prepulse inhibition in some instances) [86,88,100] may also produce varying effects.

Child/Adolescent Literature

Adolescents who have early psychotic symptoms suggestive of higher risk for developing schizophrenia have also been found to exhibit deficits in PPI, and, similar to adults, clinical improvement and treatment with medication has been associated with improved inhibition.[105,106] However, deficits were not found in medicated, euthymic, non-psychotic children with bipolar disorder[107] or in children at risk of anxiety.[108] PPI typically reaches adult levels somewhere between 8 and 9 years of age,[109-111] and again similar to adults, attention facilitates prepulse inhibition in kids.[112]

Preschool/Infant Adaptations

The presence of measurable PPI was first described for children aged 3 and 5 years.[111] Between early infancy and 5 years of age, PPI does not appear to regularly exceed 30%, in contrast to adult levels of between 50% and 75%[113]; some studies have shown nonsignificant PPI in toddlers,[114] while others have suggested that longer prepulse intervals are necessary to elicit PPI in preschoolers and infants.[115] Baseline startle magnitudes are also smaller in young children,[116] which may further increase difficulty of detection. Still other studies have suggested periods where prepulse facilitation is more likely to be found in place of PPI[117] or PPI may not have been noted at all[118] in infants and neonates.

Additionally, the small dimensions of infant's faces complicate the positioning of EMG sensors. Infants frequently display high motor activity, which may corrupt EMG recordings,[119] and they may be unwilling to tolerate procedures, particularly as they are frequently fearful of objects being positioned near the eye.[120] Even with utilization of miniature electrodes to measure EMG, a significant number of infants may need to be excluded due to lack of identifiable blinks, fussiness, or crying.[121] With traditional methods, attrition rates of 31%-50% may be seen; significantly greater than those typically seen in adult studies, usually around 5%-10%.[120]

Alternatives to the adult-standard measurement of eye blink intensity have been developed for infants. Infants' whole-body motor reaction, video quantification of infants' facial muscular contractions, and video quantification of eye-blink intensity have been used to measure PPI in infants and accurately measure latency and intensity of startle.[122] In addition, some labs

have successfully utilized eye-blink reflex intensity, successfully coding 91.7% of acoustic startle probes presented to 5 month old infants.[122] Affective modulation of startle has also been quantified in 5-month-old infants,[119,123] and term-born neonates have also been found to exhibit significant PPI.[124]

Preschoolers/Infants at Risk for Psychiatric Illness

No studies were found examining PPI in infants or preschoolers known to be at risk of later psychiatric illness.

Summary

Developmental studies of PPI are often contradictory. Some authors suggest PPI does not develop until 8 or 9 years of age, while others identify some PPI in some—but not all—subjects. Still others report young children have prepulse facilitation rather than PPI. It is encouraging that age-appropriate adaptations appear to be available. However, the optimal task parameters and typical developmental trajectory appear to remain enigmatic. Until effective task parameters can be identified for young children, use of PPI to study development in at-risk infants and preschoolers may be premature.

P50 Sensory Gating

P50 sensory gating is an evoked potential recording task wherein an adult participant lays supine in a reclined chair with his eyes open while listening to a series of paired auditory clicks with a 500 ms interstimulus interval; electroencephalographic activity is recorded. Cognitive inhibition is passively tested as the first stimulus is thought to condition or activate inhibitory mechanisms that lead to a diminished response to the second stimulus. Sensory gating is said to be "intact" when the ratio of the brain's response to the second click is significantly less than its response to the first click (test/conditioning ratio or T/C ratio of significantly less than 1.0). With intact gating, the first click should "condition" or prime the auditory system to respond in a diminished way to the second testing stimulus (Figure 5).

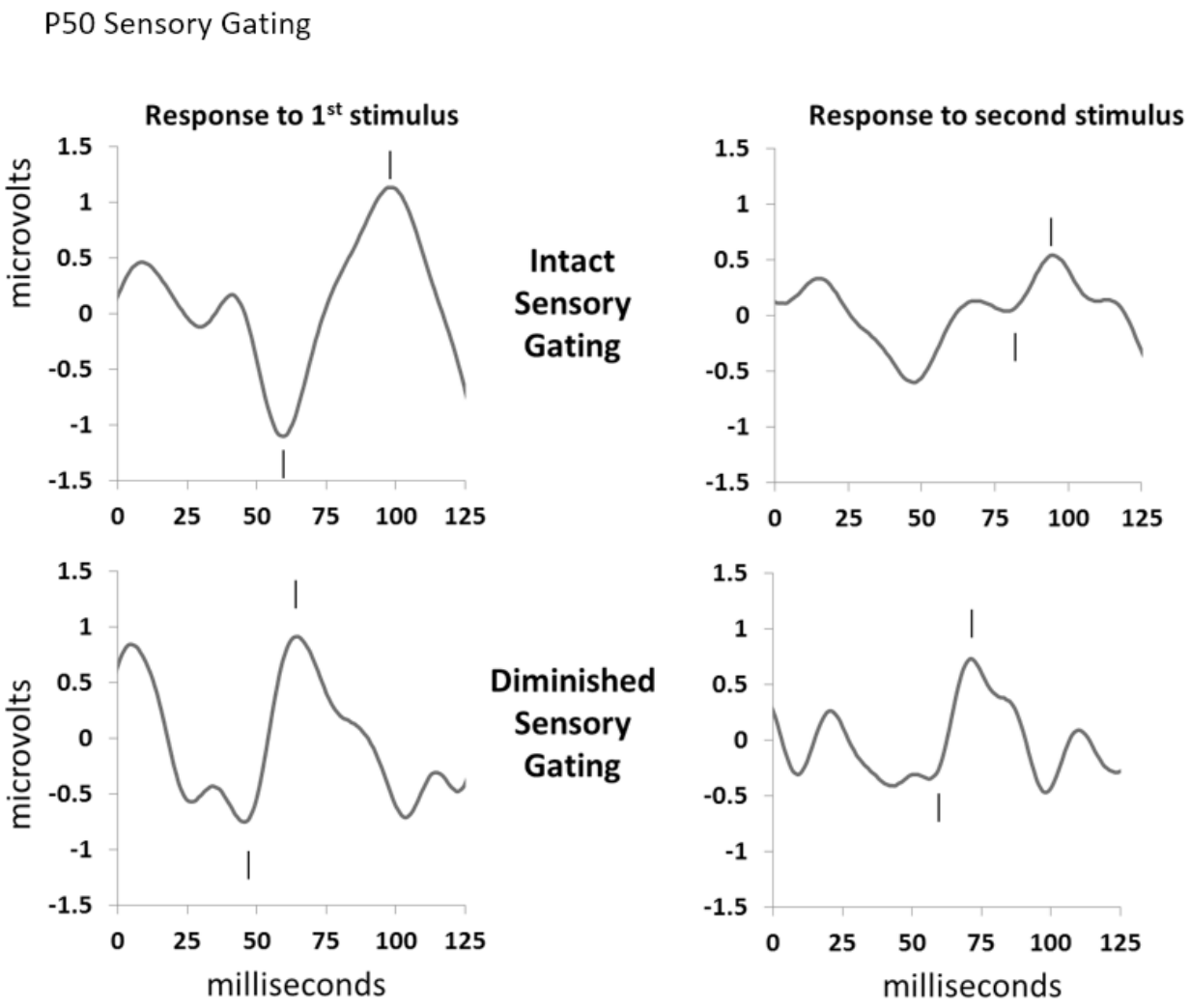

Figure 5. Example of P50 Sensory Gating. In the first row, intact cerebral inhibition (intact P50 sensory gating) is illustrated in that the response to the second stimulus (upper right) is much smaller than the response to the first stimulus (upper left). On the second row, diminished cerebral inhibition (deficient P50) is shown in that the response to the second stimulus (lower right) is very close to the response to the initial stimulus (lower left). Adapted with permission.[125]

Adult Literature

Auditory sensory gating is relatively robust in most healthy adults, with a vast majority of the population showing measurable response suppression to the test stimulus (ie T/C ratio <0.50).[126,127] Adults with schizophrenia have an impairment in sensory gating, evidenced by lack of attenuation of the test stimulus response, resulting in a higher T/C ratio.[6,15,37,128-132] This impairment has also been seen in some individuals at clinical risk of schizophrenia,[128] particularly in those with a family history of schizophrenia in a first degree relative.[133] Deficits are also seen in those with schizotypal personality disorder,[134] schizoaffective disorder bipolar type,[135] and in those with bipolar disorder with a history of psychosis.[129,135,136]

Unaffected first-degree relatives of those with schizophrenia and bipolar disorder have also been found to exhibit impaired P50 sensory gating,[15,136-138] and heritability of P50 sensory gating has been estimated at 68%.[139] In addition, P50 sensory gating has appeared to have a value in first-degree relatives that is approximately halfway between schizophrenia probands and controls, which would be predicted given their estimation of sharing approximately 50% of any abnormal genes related to schizophrenia.[138] Other factors such as clinical symptoms,[129,135,138] antipsychotic use,[129,131,133,135,138] and illness duration[131] appear to be less important, though some studies have indicated P50 suppression may be opposed by a subset of second generation antipsychotic medications, particularly clozapine[126,140,141] or worsened by increased acute symptomatology.[142,143] Smoking has been shown to acutely and transiently normalize P50 suppression in individuals with schizophrenia.[144] As such, P50 sensory gating appears to have both state and trait like components.

Of note, P50 sensory gating deficits have been validated in adults with schizophrenia during REM sleep.[145] This adaptation may decrease response variability given sensory gating's sensitivity to state dependent factors, particularly acute stress,[146,147] and attention[148] as during REM sleep noradrenergic neurons central to stress and arousal are inactive.[149] Utilizing REM, it is possible that decreased stability of P50 recordings over time previously seen[150] may be improved by decreasing state associated variability.[145]

Child/Adolescent Literature

The child literature regarding P50 is somewhat inconsistent with some reports finding maturation of the P50 response by approximately 8 to 10 years of age[151,152] and others indicating maturation through the end of adolescence.[153] It has been suggested that variability may be related to changing state-dependent factors, as previously described.

Adolescents ages 14-19 years with prodromal symptoms of schizophrenia, both with and without identified high genetic risk, have been found to have an impairment in P50 sensory gating,[154] as have younger children ages 5-10 with identified sensory processing deficits.[155] Gender[151] and current social withdrawal[156] have not been shown to influence P50 recordings in children.

Preschool/Infant Adaptations

The first issue one must address when considering performing P50 sensory gating in infants and preschoolers is state dependency. As previously noted, P50 sensory gating can be affected by acute stress. As many infants often become stressed or upset when subjected to new surroundings or to having electrodes placed on their scalps and faces, this issue is of particular importance.

Additionally, movement increases artifacts in electrophysiological recordings. Adult participants can be instructed to remain still and not to blink their eyes; however, giving verbal instructions to infants and preschoolers and expecting compliance is not possible. Attempts to restrain young children run the risk of increasing stress, thereby affecting sensory gating by increasing state change that may further, as noted above in adults, decrease the reliability of recordings over time.

For infants and preschoolers, measuring P50 sensory gating during REM sleep (termed "Active Sleep" for young infants) is an attractive possibility. Utilizing

sleep, a state in which most infants already spend a majority of their time, one is able to bypass movement and state dependent concerns. It has been noted that even though P50 (measured during active sleep) (1) occurs slightly later in infants, approximately 70 ms after the stimulus as opposed to the traditional 50 ms seen in adults, (2) improves with age even with a timespan of only months, and (3) has a broader temporal signature; inhibition of the second stimulus does occur[157] in a reliable fashion.[158] Furthermore, gating assessed in 14-week-old children was correlated to their gating at 47 months, suggesting that gating remains stable throughout early childhood.[159]

Preschoolers/Infants at Risk for Psychiatric Illness

P50 sensory gating during active sleep has been used to examine infants of mothers with anxiety as compared to infants whose mothers did not have psychiatric comorbidity, yielding that infants whose mothers experienced anxiety had poorer P50 sensory gating, an effect mitigated by anti-depressant use.[160] Infants at higher risk for schizophrenia secondary to having parents with psychosis, compared to non-smoking mothers without psychiatric illness, have decreased inhibitory gating utilizing the P50 paradigm.[161] Improved infant P50 sensory gating development is also associated with perinatal choline supplementation.[162]

Summary

P50 sensory gating appears to be the task that, thus far, has been the most translated and utilized in younger populations at risk of disease. In adults and adolescents, the task has been more rigorously defined, has been associated with psychosis, and its genetic risk has been more clearly delineated.

It is interesting to note how this consensus occurred. Through meta-analysis, it was determined that there is a relationship between stimulus intensity and the effect size between individuals with schizophrenia and comparison subjects.[137] With larger multi-site trials, a unified protocol including lower sound intensity, subjects placed in a recumbent position, and a beta to gamma (10-100hz) EEG frequency band-pass filter, a resolution of site differences was able to occur. It may be that similar data review in other tasks will lead to unification of apparent discrepancies thus far seen in younger age groups.

The findings that state associated features may be reduced by recording during REM sleep makes this task particularly attractive for use in infants. As such, it has been successfully used in infants of mothers with mood and anxiety disorders and infants of parents with psychosis. It is clear that infant research is possible. It would be interesting to continue to extend these findings to older age groups and to follow the change in symptomatology associated with impaired P50 sensory gating over time. For example, it has been shown that impaired P50 sensory gating as an infant has been associated with more attentional problems at age 3.3 years as measured by the child behavior checklist.[163]

Discussion

Most neuropsychiatric disorders are presumed to be neurodevelopmental in nature, where onset of symptoms is the end result of a decades-long interaction between genetic and environmental factors. There are 2 presumed critical developmental windows relative for psychosis: prenatal and adolescent. Abnormalities in prenatal brain development lead to vulnerability and, in some individuals with already vulnerable brains, further abnormalities in adolescent brain development result in conversion from vulnerability to illness.[1,2] One of the major corollaries of this hypothesis is that while onset of more specific and severe illnesses, such as psychotic illnesses, requires adverse development during both critical developmental windows, abnormal development during the prenatal window alone increases lifelong risk for significant other types of cognitive and functional impairment including attentional and social dysfunction, even if the later adolescent impairment in brain development never occurs.[164-170] Another way of saying this is that abnormal prenatal neurodevelopment non-specifically increases risk for a wide range of neuropsychiatric and cognitive disorders. This sometimes leads to the concern that non-specificity of risk limits the potential benefit of early use of biomarkers. However, non-specificity also provides an opportunity for understanding and, with intervention, prevention across a breadth of disorders. The malleability of the brain during early developmental period makes it a potentially ideal time to intervene, with intervention lasting only a few months having potential life-long ramifications.

Another related potential risk of early developmental biomarkers is the risk that what appears to be the same measure (eg disruption of smooth pursuit) at different ages may not reflect the same neurobiology. Thus, longitudinal approaches and converging evidence across different study formats are a necessary step towards accurate interpretation of early developmental biomarkers.

The National Institute of Mental Health has called for an increase in research focusing on the developmental aspects of biological markers, and this review highlights the relative lack of research in this area. Several psychophysiological tasks are, in older children and adolescents, associated with an increased risk of later onset illness, and some of the tasks appear to be ready for research use in infants and preschoolers. P50 sensory gating and smooth pursuit eye movements already have early literature suggesting their utility in very young populations. The antisaccade task and prepulse inhibition may also have utility, although further work adapting methodology to young children is necessary (Figure 6).

Conclusion

The charge to investigate the development of psychiatric disease throughout the lifespan may initially sound intimidating. Working with infants and preschoolers means more variability, and with more variability (and frequently lower or smaller responses and rates), an increased capacity to detect differences must be present. Before undertaking this task, one would first want to ensure that deficits are present, have been associated with risk of later onset disease, have developmentally appropriate correlates, and the tasks utilized in older populations are usable in pre-

	Task Assoc. with Risk of Disease	Indication of Heritability	Dev. Appropriate Tasks Available	Parameters Defined	Used in at Risk Populations
Anti-Saccade	X	X	X	X	
Pre-Pulse Inhibition	X	X	X		
P50 Gating	X	X	X	X	X
SPEM	X	X	X	X	X

Figure 6. Graphic representation of task conclusions. As illustrated with an X, the antisaccade, prepulse inhibition, P50 sensory gating, and smooth pursuit eye movement (SPEM) tasks all have been associated with risk of later onset disease, are heritable, and have developmentally appropriate versions available for use in infants and preschoolers. Antisaccade, P50, and smooth pursuit further appear to have developmental and specific task parameters more defined, and P50 and SPEM have also seen some preliminary research done in populations at risk of developing psychiatric disease using adaptations.

schoolers and infants. In several of the tasks described above, we believe that this is the case.

Historically, investigators have also been hesitant to perform research on infants and young children because of lack of specificity regarding disease outcome. The NIMH's proposal for novel ways to approach psychiatric disease diminishes these concerns.

If we are to decrease morbidity and mortality associated with risk factors for psychiatric disease and begin to consider primary prevention of psychiatric illness, research in younger age groups including infants and preschoolers is of paramount importance. Utilizing adaptations of traditional adult tasks, this research is also now possible.

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Sleep Spindles and Auditory Sensory Gating: Two Measures of Cerebral Inhibition in Preschool-Aged Children are Strongly Correlated

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Abstract

Introduction. Sleep spindles and P50 sensory gating are both reflective of cerebral inhibition, however, are differentially active during different phases of sleep. Assessing whether sleep spindles and P50 sensory gating correlate is a first step to evaluate whether these 2 forms of cerebral inhibition reflect overlapping neural circuits.

Methods. EEG data were collected between midnight and 6:00 AM on 13 healthy preschool-aged children. P50 sensory gating, calculated during REM sleep, negatively correlated with spindle duration (r=-.715, p=.006) and inter-peak density (r=.744, p=.004). There was a trend toward higher S2/S1 ratios being associated with fewer peaks per spindle (r=-.546, p=.053). In 4-year-olds, 2 established physiological measures of sensory gating and are correlated despite being maximally active during different stages of sleep.

Conclusions. These results suggest there is an overlap in brain mechanisms underlying each gating mechanism.

At any moment, a vast amount of sensory information is being captured by peripheral modalities and has the potential to reach the cerebral cortex, where it can be processed and acted upon. Much of this information is extraneous, and thus reducing ("gating") transmission of irrelevant sensory information is necessary in order to avoid overburdening cortical processing capabilities. This is particularly true during sleep, where cortical processing of external stimuli has to be limited to the most critical sensory information. While sensory gating occurs during multiple stages of sleep, there has been little effort to explore correlations between gating across stages: does sensory gating ability at one stage of sleep predict sensory gating during another stage? A correlation between different gating mechanisms would suggest overlapping neural mechanisms of gating and provide support for exploring common etiologic factors. We focus here on 2 sensory gating processes that are both thought to include thalamic interneurons,[1,2] but which are prevalent at different sleep stages: sleep spindle generation, which is limited to Stage 2 non-Rapid Eye Movement (NREM) sleep; and P50 sensory gating, which is maximally effective while awake and during Rapid Eye Movement (REM) sleep. A sample of convenience of overnight electroencephalograms from healthy 4-year-olds was utilized in this initial study.

Sleep spindles are characteristic brief 11-15 Hz waveforms on EEG with a progressively increasing then decreasing amplitude that are specific to the sleeping state.[3] They are generated by GABAergic neurons in the thalamic reticular nucleus (TRN)[4] and are believed to reflect neuronal connectivity patterns in corticothalamic and thalamocortical circuits.[3,5] Ninety percent of TRN neuronal projections are to thalamocortical neurons; activation of TRN neurons inhibits signal transmission to the cerebral cortex.[6] This thalamic spindle production by cortex-

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stimulated reticular cells gates sensory input while sleeping, allowing the brain to resist waking in the face of disruptive external sensory stimuli.[7, 8]

P50 auditory sensory gating refers to a reduction in an early evoked response in the face of repetition of an auditory stimulus. In the most commonly utilized form of the task, an individual is exposed to 2 identical auditory stimuli occurring 500 ms apart. The amplitude of early components of the evoked response is reduced in response to the second stimulus relative to the first.[9] One common quantification of this effect is to measure the ratio of the amplitudes of the P1 wave, which in adults occurs approximately 50 ms after both the first (S1) and second (S2) stimulus. Intact auditory sensory gating is indicated by a reduction in the amplitude of the evoked P1 wave to the second stimulus that yields a ratio significantly less than 1. P50 sensory gating (ratios closer to 0) occurs during REM sleep but is absent (ratios closer to 1) in NREM sleep.[10] P50 sensory gating can be identified in newborns[11] and appears to be fully developed within a few months after birth.[12] P50 sensory gating has been linked to GABAergic neurons[13, 14] and involves a circuit which includes the thalamus, hippocampus, and prefrontal cortex.[2]

Sleep spindles have been found to mediate sleep maintenance,[15] memory consolidation,[4,8,16-19] and cortical development during sleep,[5] among other functions, and reduced spindle activity is thought to be a reflection of inherent thalamic dysfunction as well as thalamic responsiveness to cortical stimulation. Poor sleep spindle generation in 5-year-olds predicts more externalizing behavior and more peer problems 1 year later.[20] In a similar fashion, poor auditory sensory gating in infants has been associated with later problems in attention, anxiety, and externalizing symptoms at 40 months of age,[21] and it has been postulated that diminished sensory gating in infants may reflect an increased risk for later psychopathology.[22-24] fMRI studies also suggest that the thalamus is involved in sensory gating.[2,25] For both sleep spindles and P50 sensory gating, the thalamic reticular nucleus is thought to be responsible for the thalamic response during the gating tasks,[2,6,19] where dysfunction in GABAergic neurotransmission leads to impaired sensory inhibition.[4,13,14]

Sleep spindles and P50 sensory gating are both thought to reflect activity of GABAergic neurons and are also both thought to involve the thalamus, yet the 2 measures reflect activity during different sleep stages (Stage 2 for sleep spindles and REM for P50 gating). This raises the question of whether or not the 2 inhibitory processes are correlated—we hypothesize that they are. We have previously reported on overnight P50 sensory gating scores in 4-year-old children as part of a process to determine stability between infant and 4-year-old performance during REM sleep. That study suggested that P50 sensory gating matured to adult levels within a few months after birth and that analysis of 4-year-old results may be generalizable to other ages.[26] The current study adds an analysis of sleep spindles during the same overnight recording with the goal of investigating the relationship between 2 measures of cerebral inhibition, sleep spindles and P50 auditory sensory gating. This is the first study to investigate such a relationship and would contribute to the effort to understand the relationship between sensory gating mechanisms.

Method

Participants

Fourteen preschool-aged children (9 females) who were part of a longitudinal study on early child development in a large metropolitan area and who were within 2 weeks of their fourth birthday were recruited for an overnight sleep study aimed at testing P50 auditory sensory gating stability from birth to 4 years of age. Artifact-free data with minimums of 30 minutes of REM and 3.5 hours of total sleep was considered the minimum amount necessary for analysis. Data from 1 participant (1 female) is excluded because there was insufficient artifact-free data. The mean age for the remaining participants in this study is 47.15 (SD=0.99) months. Additional demographic information is summarized in Table 1. This was a healthy pediatric sample, which had been followed since infancy.

Procedure

All procedures involving human subjects were approved by the Colorado Multiple Institute Review Board (COMIRB), and parents of the participants gave written informed consent. Participants were admitted for an overnight stay to a pediatric clinical research center at a local children's hospital. All participants were screened prior to admission for acute illness,

and once admitting procedures were complete, were provided dinner and access to entertainment until bedtime. Parents of participants were encouraged to follow the child's typical bedtime routine. One parent remained in the room with the child overnight.

Electroencephalographic Recordings

Ag/AgCl electrodes (Grass; West Warwick, Rhode Island, USA) filled with Ten20 conductive paste (DO Weaver; Aurora, Colorado, USA) were attached to the sleeping child with adhesive medical tape. EEG and auditory-evoked potentials were recorded from the vertex of the scalp (Cz). For aid in sleep staging, bipolar electrooculogram (EOG) was recorded from electrodes directly superior and lateral to either the left or right eye; submental electromyogram (EMG) was also recorded. Times of movement and environmental events were also noted. Signals were recorded using NuAmps (Neuroscan Labs, Sterling, Virginia, USA). EEG signals were amplified 5000 times and filtered between 0.05 and 100 Hz; EOG signals were amplified 1000 times and filtered between 1 and 200 Hz; and EMG signals were amplified 10,000 times and filtered between 1 and 200 Hz. Sampling rate occurred at 1000 Hz. Stimulus presentation (for assessment of P50 auditory sensory gating) and recording began when the electrode impedances were below 10 kΩ. The longest periods of REM (the stage for the reliable assessment of P50 sensory gating) and Stage 2 (the period most associated with sleep spindle activity) sleep occur in the early morning hours; thus, data collection did not begin until 11:00 PM and continued until approximately 6:00 AM.

The data were converted from the Scan 4.1 software (Neuroscan Labs; Sterling, Virginia, USA) format to ASCII format so that further analysis using MatLab (Mathworks; Natick, Massachusetts, USA) software could be conducted. A visual representation of EOG, EMG, and EEG activity was generated and provided a global view of each participant's sleep cycles (Figure 1A). Sleep staging was completed based on the criteria of Anders et al.[26] REM sleep was identified by the presence of rapid eye movements obtained on EOG, low amplitude in the EMG, and low amplitude high frequency in the EEG. Stage 2 NREM sleep was identified by the absence of rapid eye movements as obtained by EOG, increased amplitude in the EMG, and the presence of sleep spindles. Sleep state was then verified by visual inspection of the continuous recording in 20-s epochs.

Sleep Spindle Analysis

Spindle detection was performed by applying a band-pass filter between 11-15 Hz. A baseline average amplitude was calculated from spindle-free EEG and a threshold value of 2.5 times the baseline average was used for automated identification of spindle cycles. Likewise, the beginning and end of each spindle was determined by an increasing or decreasing peak amplitude that fell below 2.5 times the baseline average. Automated selection was confirmed by visual inspection of the EEG record (Figure 1B). Measurements of spindle duration in milliseconds and the number of individual peaks per spindle were obtained. Mean inter-peak interval (calculated as number of peaks per spindle divided by spindle duration) was used as a measure of spindle density. Spindles occur as a series of electroencephalographic peaks; more peaks per spindle, a longer spindle duration, and a lower inter-peak interval (greater density of peaks) are evidence of increased spindle activity and reflect increased sensory gating.

P50 Auditory Sensory Gating Analysis

Methods for P50 sensory gating assessment in children have been previously described in detail,[12] and will briefly be reviewed here. Paired clicks were presented through 2 speakers positioned on either side of the bed at a distance of .50 m from each ear. Volume was adjusted so that each click was at 85-dB sound pressure level at the ear. The clicks were delivered continuously throughout the overnight study for each subject. The first 20 minutes of the longest-recorded REM cycle was used for analyses. This length of time was selected because it yields an adequate number of stimuli for analysis and reduces variability caused by individual differences in sleep.[27]

Single-trial-evoked potentials were extracted from 100 ms before each click to 200 ms following each click. Trials were excluded in which the signal on the recording of identified periods exceeded ±75 mV. The average waveforms from single trials were band pass filtered between 10 and 50 Hz to accentuate middle latency components. For each subject, the largest positive peak between 50 and 100 ms after an auditory click (P50) preceded by a negative trough was

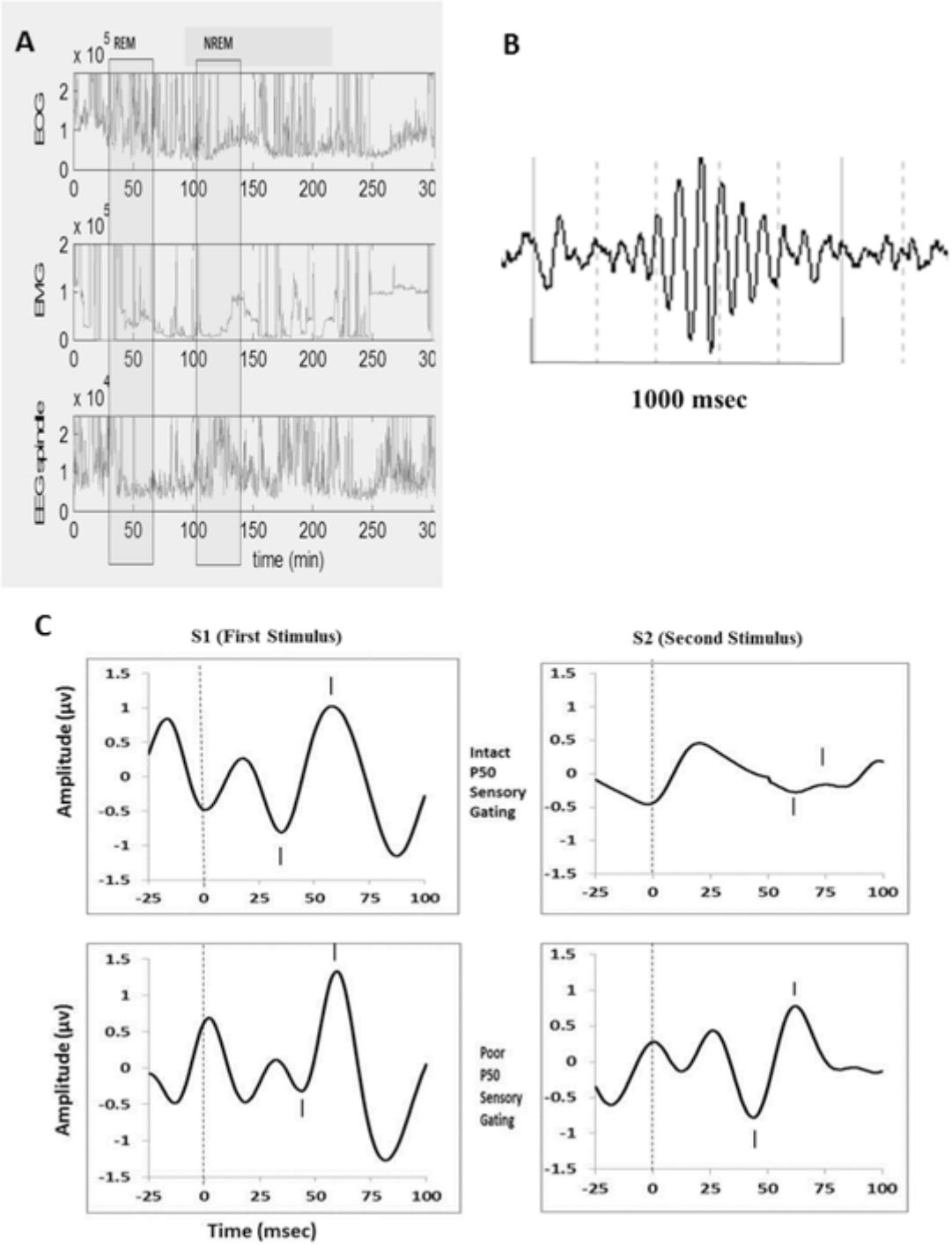

Figure 1. (A) Graphical representation of a 5-hour sample drawn from overnight EEG, EOG, and EMG activity recorded from a participant. A period of REM has been highlighted to show increased EOG activity and decreased EMG and EEG spindle activity indicative of this stage of sleep. A period of Stage 2 NREM activity has been highlighted to demonstrate increased spindle activity in the EEG accompanied by decreased EOG activity. (B) An example of a sleep spindle recorded from the vertex. This image is representative of spindle activity following the application of an 11-15 Hz bandpass filter. This particular spindle had 6 peaks with a mean inter-peak interval of 73.33 ms. (C) P50-evoked potential tracings. Two stimuli are presented 500 ms apart (noted by the 2 time 0s in any horizontal pair of panels). The P50 response is delineated by hash marks. Intact sensory gating is demonstrated on the top half of this figure. Note the size of the evoked response to the first stimulus, S1 (1.86 µv) and the corresponding response to the second stimulus, S2 (.11 µv). The resulting S2/S1 ratio is 0.06. Poor P50 sensory gating is demonstrated on the bottom half of this figure. The amplitude of the response to the first stimulus, S1 was 1.64 µv while that for S2 was 1.05 µv. The resulting S2/S1 ratio is 0.64.

identified and measured, peak to trough, by a computer algorithm.

For each child, a mean response latency and amplitude of the P1-evoked potential wave to each stimulus (S1 and S2) were calculated. In addition, their ratio was calculated by dividing the amplitude of the P1-evoked response to S2 by the amplitude of the P1-evoked response evoked by S1. A ratio closer to 0 is indicative of robust sensory gating, while a ratio closer to 1 is indicative of diminished sensory gating (Figure 1C).

Statistical Approach

Descriptive data was calculated for spindle measures (duration and density) and P50 auditory sensory measures (amplitudes, latencies, and gating ratio). Bivariate correlational analyses were used to assess the relationship between spindle duration, number of peaks per spindle, and spindle density and measures of P50 auditory sensory gating. IBM SPSS Statistics for Windows, Version 22 (Released 2013, Armonk, NY: IBM Corp.) was used for all analyses.

Results

The mean length of artifact-free sleep data was 4.76 (SD=.64) hours (Range: 4.06–5.96 hours). The mean length of REM sleep data was 57.77 (SD 8.96) minutes (Range 44-69 minutes). Table 1 summarizes the primary electrophysiological measures of interest.

P50 gating ratios were positively correlated with spindle density (r=.744, p=.004), negatively correlated with spindle duration (r=-.715, p=.006) and trended towards a negative correlation with mean inter-peak interval (r=-.546, p=.053) (Table 2 and Figure 2).

Discussion

One of the brain's most important functions is to inhibit its own signals in order to filter out irrelevant sensory information. It utilizes a number of mechanisms to achieve this goal including 2 processes active during sleep: sleep spindle generation and P50 sensory gating. While thalamic GABAergic inhibition has been postulated to contribute to both inhibitory mechanisms, there has been little investigation of whether performance of one process correlates to the other. In this study, we examined the relationship, in preschool-age children, between 2 measures of cerebral inhibitory functioning that had not been compared before, P50 sensory gating and sleep spindles. Elevated P50 gating ratios, corresponding to impaired auditory gating, were associated with shorter spindle duration as well as increased intra-spindle density (lower mean inter-peak interval).

P50 sensory gating and sleep spindles are maximally active at different stages of sleep, suggesting, on the surface, that they are the product of different neurological circuits. However, our results demonstrating the correlation between the processes are more consistent with the hypothesis that GABAergic thalamic interneurons contribute to both processes. As the TRN functions as the spindle pacemaker, with spindle rhythm persisting in decorticated animals but disappearing after thalamic destruction,[5] both intrinsic thalamic cells and their connections to and from the cortex are implicated in diminished gating.

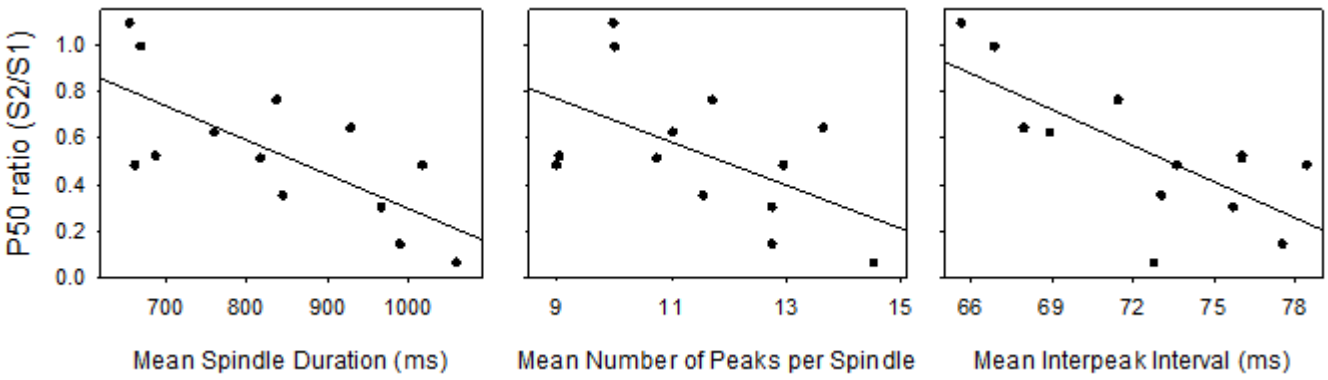

Figure 2. Scatterplot showing correlation of P50 ratio (S2/S1) and (A) mean spindle duration (r=-.715, p=.006), (B) number of peaks per spindle cycle (r=-.546, p=.053), and (C) mean inter-spindle interval (intra-spindle density) (r=-.728, p=.005).

An alternative method for examining interrelationships between these 2 sleep-associated gating mechanisms would have been to focus on individuals with deficiencies in cognitive functions that have previously been associated with abnormal sleep spindles and P50 measurements, including attention, executive functioning, and working memory. These 2 sensory gating deficits are present in a range of neurodevelopmental disorders including schizophrenia,[7,9,16,19,28-30] autism spectrum disorders,[31-33] and ADHD.[34] However, even if a correlation between these 2 physiologic measures had previously been elucidated in neuropsychiatrically-ill subjects, it would be difficult to interpret the results. It would be unclear whether these measurements would correlate due to overlapping functional circuits or whether the correlation was a result of similar effects on both processes due to medication treatment or cognitive sequelae of the disease. P50 sensory gating matures to adult levels within a few months after birth[27] and is stable after that point.[26] Spindle activity also is relatively stable, at least from late preschool years through mid-adolescence.[35] Thus, although the pediatric population investigated in this study was a sample of convenience, generalizability to older populations may be reasonable. In addition, an advantage of studying young children is the ability to study processes prior to onset of treatment and prior to the effects of years of having to live with the disease. Establishing that these 2 measures represent the same underlying pathology may guide future studies in clarifying the mechanism behind these faulty inhibitory brain processes.

While not the primary purpose of this report, an important goal in the investigation of inhibitory processes could be to contribute to the identification of biophysiological risk factors for neurodevelopmental disorders. Lower spindle activity and poor P50 sensory gating each are predictive of both later neurocognitive and behavioral difficulties.[20,21] If sleep spindles and P50 auditory gating are indeed correlated and represent the same underlying pathology as our results suggest, concurrent evaluations of both processes may provide better predictive ability than either assessment alone. Future research would be required to assess this possibility. In addition, as this study was done only in young children, future research may also investigate the effect of age on the correlation between sleep spindles and auditory gating.

Conclusion

P50 sensory gating and sleep spindle both function to gate sensory information; however, during sleep, spindle generation is strongest during Stage 2 slow wave sleep, while P50 sensory gating is most active during REM sleep. The correlation between P50 gating ratios and sleep spindles, 2 physiological measures of sensory gating, suggest that, despite the fact that the 2 measures occur during different stages of sleep, these 2 processes may share some underlying neurocircuitry. GABAergic thalamic neurons are one possible contributor to both processes.

Author Note

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Table 1. Demographics, Spindle, and P50 Characteristics

Demographics	**N (%)**
Female:male	8:5 (62:38)
Caucasian Hispanic	2 (15)
Caucasian Non-Hispanic	11 (85)
	Mean (SD)
Maternal Socioeconomic Status (SEI)[a]	55.38 (26.79)
Age (months)	47.15 (.99)
Spindle Characteristics	**Mean (SD)**
Spindle Duration	838 (144) msec
Number of peaks per spindle	11.5 (1.75)
Inter-peak interval	72.65 (4.19) msec
P50 Characteristics	**Mean (SD)**
S2 (test) amplitude	1.39 (1.04) μV
S1 (conditioning) amplitude	2.58 (1.36) μV
S2/S1 ratio	0.534 (0.297)
S2 latency	67.31 (7.94) msec
S1 latency	64.2 (8.03) msec

[a]The Socio-economic Index (SEI) of Occupations[36] includes 503 occupations scored in a potential range of 0-100. Managerial and professional occupations generally have scores above 60; technical, sales, and administrative support occupations generally score between 35 and 60; service, agricultural, and labor occupations generally have scores below 35; never employed single individuals are assigned a score of 0. Values reported are for the highest occupation value achieved across an individual's life.

Table 2. Correlations between P50 components and spindle characteristics
S1, First stimulus in P50 measure; S2, Second stimulus in P50 measure p<.05

	Spindle Duration		Number of peaks per spindle cycle		Inter-peak interval (Intra-spindle density)	
	Pearson Correlation (r)	Significance (p)	Pearson Correlation (r)	Significance (p)	Pearson Correlation (r)	Significance (p)
S1 amplitude	-.044	.885	-.134	.662	.195	.524
S2 amplitude	-.484	.094	-.424	.149	-.364	.221
S1 latency	-.201	.511	-.286	.343	.147	.631
S2 latency	.226	.458	.177	.562	.162	.596
P50 ratio (S2/S1)	-.715	.006[a]	-.546	.053	-.728	.005[a]

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Amanda K. Hutchison, MD is a child, adolescent and adult psychiatrist in private practice in Denver, Colorado. Dr Hutchison has had an interest in child psychiatry since undergraduate and has worked on research related to mood and attention disorders in preschool children using cognitive and play therapy-type methodologies. She has specific interests in doing psychotherapy with children and adolescents.

Dr Hutchison received her bachelor's degree in Psychology from the University of Colorado, Boulder and her medical degree from the University of Colorado, Denver. She completed her residency in adult psychiatry and fellowship in child and adolescent psychiatry at the University of Colorado Denver and Children's Hospital Colorado. She recently completed a 2-year program in psychodynamic psychotherapy through the Denver Institute for Psychoanalysis and started a 4-year training program for child and adult psychoanalysis in the Fall of 2016.

Laura Judd-Glossy, PhD; Author

Laura Judd-Glossy, PhD is an assistant professor in the Department of Psychiatry at the University of Colorado School of Medicine. She serves as a pediatric psychologist on the Child Psychiatry Consultation-Liaison Service at the Children's Hospital Colorado. Dr Judd-Glossy provides consultation and liaison services to pediatric patients and their families who are admitted for inpatient medical hospitalization. She provides clinical supervision and training for psychology interns, psychiatry fellows, and medical students on the Consultation-Liaison Service. Dr Judd-Glossy's research interests focus on how youth and families manage pediatric acute and chronic medical illness, with her most recent research being on the etiology, assessment, and treatment of non-epileptic seizures.

Dr Judd-Glossy received her bachelor's degree in Psychology from the College of William and Mary, her master's degree in School Counseling from Boston College, and her doctoral degree in School Psychology from the University of Texas at Austin. Dr Judd-Glossy completed her predoctoral internship at Boston Children's Hospital/Harvard Medical School. As a postdoctoral fellowship at Dana-Farber Cancer Institute/Harvard Medical School, she specialized in the clinical treatment of pediatric oncology/hematology patients and survivors.

Harpreet Kaur, PhD; Author

Harpreet Kaur, PhD is a clinical assistant professor at the University of Arizona, College of Medicine and serves as the Consultation Liaison Psychologist at Phoenix Children's Hospital. Dr Kaur provides psychological services in an inpatient medical setting to children and adolescents with chronic and acute medical conditions. She provides supervision and training to psychology interns on the consultation liaison service. Dr Kaur also provides lectures to advanced nursing students about cognitive behavioral therapy and mindfulness in a pediatric setting. Her research interests include understanding symptom presentation in ethnically diverse youth exposed to trauma and examining the effectiveness of evidence-based interventions in health care settings.

Dr Kaur received her bachelor's degree in Psychology and Biology from Whittier College and her doctoral degree in Clinical Psychology from the University of Nevada, Las Vegas. She completed her postdoctoral fellowship in the Medical Day Treatment program at Children's Hospital Colorado.

Sarah L. Kelly, PsyD; Author

Sarah L. Kelly, PsyD is an assistant professor in the Departments of Pediatrics and Psychiatry at the University of Colorado School of Medicine. She serves as the Pediatric Psychologist for the Heart Institute at Children's Hospital Colorado and provides psychological assessment, intervention, and consultation across the outpatient cardiology clinic, subspecialty multidisciplinary clinics, and inpatient cardiac intensive and progressive care units. She is the Clinical Director of the Heart Institute Wellness Program, formed to optimize the comprehensive psychosocial healthcare of children with congenital and acquired heart disease. Her research interests include the psychological adjustment and health-related quality of life of high-risk cardiac populations, and she is involved with the Cardiac Neurodevelopmental Outcome Collaborative (CNOC) and the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC).

Dr Kelly received her bachelor's degree in Psychology from Miami University of Ohio and her master's and doctoral degrees in Clinical Psychology, with a child and adolescent concentration, from Wheaton College, Illinois. She completed her predoctoral psychology internship at Denver Health Medical Center and a pediatric psychology postdoctoral fellowship at Children's Hospital Colorado in pediatric solid organ transplant surgery.

Jessica Malmberg, PhD; Author

Jessica Malmberg, PhD is an assistant professor of psychiatry and pediatrics at the University of Colorado School of Medicine and works as a clinical psychologist in the Pediatric Mental Health Institute and Neuroscience Institute at Children's Hospital Colorado. She also serves as the Clinical Director of Outpatient Services in the Pediatric Mental Health Institute. She is a course director for an interdisciplinary didactic on pediatric behavioral medicine, supervises psychology and psychiatry trainees, and leads a training group for children with disruptive behavior disorders. Dr Malmberg provides outpatient behavioral health services to children, adolescents, and families presenting with a wide spectrum of behavioral health disorders. She has strong research and clinical interests in disruptive behavior disorders, parenting interventions, chronic pain conditions, and functional disorders. Dr Malmberg is heavily involved in innovative program development and dissemination efforts to bring a transdiagnostic approach to pediatric behavioral health assessment and treatment services.

Dr Malmberg received her master's degree in Psychology, her educational specialist degree in School Psychology, and her doctoral degree in Combined Clinical/Counseling/School Psychology, with a specialization in clinical child psychology, from Utah State University. She completed her predoctoral internship at Children's Hospital Colorado in pediatric health psychology and a postdoctoral fellowship at the Cleveland Clinic Children's Hospital in pediatric psychology

MaryAnn Morrow, PMHNP-BC; Author

MaryAnn Morrow, PMHNP-BC is an instructor at the University of Colorado School of Medicine and is an outpatient psychiatric provider with the Pediatric Mental Health Institute (PMHI) at Children's Hospital Colorado. She is responsible for diagnostic and medication management for children and adolescents in the outpatient psychiatric clinic. In addition to seeing patients and their families, she precepts student nurse practitioners. Ms Morrow is interested in research concerning Non-Suicidal Self Injury (NSSI) and ongoing information concerning diagnosis and treatment of children with Autism Spectrum Disorders.

Ms Morrow received her bachelor's degree in Nursing from the Mayo Clinic in Rochester, Minnesota and her master's degree in Business Administration from Washington University in St Louis, Missouri. She studied for both her master's degree and the psychiatric mental health nurse practitioner degree at the University of Colorado, and is now board certified as a PMHNP-BC.

Benjamin Mullin, PhD; Reviewer

Benjamin Mullin, PhD is an assistant professor of psychiatry at the University of Colorado School of Medicine and a psychologist in the Pediatric Mental Health Institute's outpatient clinic at Children's Hospital Colorado. Dr Mullin provides short-term, evidence-based individual and group therapy to youths with acute and disabling anxiety. Dr Mullin also provides training for clinical psychology externs, interns, and psychiatry residents on evidence-based treatments for anxiety, tics, and sleep disorders. Dr Mullin's research focuses on the pathophysiology of anxiety disorders among youth, and in particular, how sleep disruption may precipitate emotion dysregulation by altering activity in key neural circuits.

Dr Mullin received his bachelor's degree in Psychology from Clark University and his master's and doctoral degrees in Clinical Psychology from the University of California, Berkeley. He completed a 2-year research fellowship in sleep medicine and translational neuroscience at the University of Pittsburgh School of Medicine and a 1-year fellowship in pediatric anxiety disorders at Children's Hospital Colorado.

Douglas K. Novins, MD; Reviewer, Editor-in-Chief

Douglas K. Novins, MD is the Cannon Y. & Lydia Harvey Chair in Child and Adolescent Psychiatry, and Chair of the Department of Psychiatry & Behavioral Sciences at Children's Hospital Colorado. He is also professor of psychiatry and community & behavioral health at the University of Colorado Anschutz Medical Campus. Dr Novins serves as the leader of child and adolescent behavioral health at Children's Hospital Colorado and the University of Colorado Anschutz Medical Campus, leading the ongoing development of a diverse set of clinical, training, and research programs with over 60 faculty and 275 staff. Dr Novins' expertise is in the areas of adolescent substance-related problems and traumatic experiences, particularly among American Indian and Alaska Native youth. He is also Deputy Editor of the *Journal of the American Academy of Child & Adolescent Psychiatry* (JAACAP), the highest ranked publication in child and adolescent psychiatry and developmental psychology. He was recently selected to be the 7th Editor-in-Chief of JAACAP with the first issue of his term scheduled to be published in January, 2018.

Dr Novins received his bachelor's degree in History and Premedical Studies from Columbia College and his medical degree from Columbia University's College of Physicians and Surgeons. He trained in general psychiatry at New York University/Bellevue Hospital and in child and adolescent psychiatry at the University of Colorado. The National Institute of Mental Health supported Dr Novins' research training at the University of Colorado through a postdoctoral research fellowship in developmental psychobiology and a career development award in mental health services research.

Philip C. O'Donnell, PhD; Reviewer

Philip C. O'Donnell, PhD is an assistant professor in the Department of Psychiatry and Behavioral Sciences at Northwestern University and the Director of the Cook County Juvenile Court Clinic. Prior to joining Northwestern's faculty, Dr O'Donnell was an assistant professor of psychiatry at the University of Colorado School of Medicine and the Clinical Director of the Intensive Psychiatric Services program at Children's Hospital Colorado. Dr O'Donnell has specialized training in the forensic assessment of children and families and has served as an expert witness and consultant to judges, attorneys, caseworkers, and probation officers in California, Colorado, and Illinois.

Dr O'Donnell received his bachelor's degree in Psychology from Creighton University, and his doctoral degree in Clinical Psychology from Loyola University Chicago. He also holds a master's degree in Jurisprudence, Child and Family Law, from Loyola University Chicago's School of Law. He completed a postdoctoral fellowship in forensic psychology at the University of Southern California's Institute of Psychiatry, Law, and Behavioral Sciences.

Lina Patel, PsyD; Author

Lina Patel, PsyD is an assistant professor of child and adolescent psychiatry at the University of Colorado School of Medicine, practicing at Children's Hospital Colorado. Dr Patel is the Director of Psychology for the Anna and John J. Sie Center for Down Syndrome, a multidisciplinary consultative clinic coordinating care for infants, children, teens, and young adults with Down syndrome. Dr Patel is responsible for the management of all referrals for psychological treatment and evaluation. She provides consultation with schools, parent training regarding the management of challenging or unsafe behaviors, evaluation for dual diagnoses (Down syndrome and Autism), toilet training, and desensitization to medical devices (such as hearing aids and CPAP) and procedure-related distress. Outside of her clinical work, she has presented to numerous organizations across the country with a focus on behavioral interventions with individuals with Down syndrome. She also conducts research on clinical issues impacting those with Down syndrome.

Dr Patel received her bachelor's degree in Psychology from the University of Oklahoma and her master's and doctoral degrees in Clinical Psychology from the University of Denver's Graduate School of Professional Psychology. She completed her internship training at Boston University Medical Center and her postdoctoral fellowship at Stanford University's Lucile Packard Children's Hospital.

Randal Ross, MD; Author

Randal Ross, MD, who passed away as this issue of the Journal was coming to press, was the L. McCarty-Fairchild Professor of Child Psychiatry in the departments of Psychiatry and Pediatrics and the Director of the Schizophrenia Research Center at the University of Colorado School of Medicine. Dr Ross served the University of Colorado School of Medicine for 24 years and directed research training programs for undergraduates, medical students, general psychiatry residents, child and adolescent psychiatry residents, and postdoctoral trainees. His research focused on understanding the developmental pathway to psychiatric illnesses, including schizophrenia and ADHD, and development and testing of novel primary prevention strategies.

Dr Ross received his bachelor's degree in Physiological Psychology from the University of California, Santa Barbara and his medical degree from Yale University. He completed both general and child and adolescent psychiatry residencies at the University of Washington in Seattle, Washington. Dr Ross received research postdoctoral training from the Developmental Psychobiology Research Group at the University of Colorado School of Medicine.

Elise M. Sannar, MD; Author

Elise M. Sannar, MD is an assistant professor of psychiatry at the University of Colorado School of Medicine, practicing at Children's Hospital Colorado. Dr Sannar is one of 2 attending psychiatrists on the Neuropsychiatric Special Care Unit (NSC), an intensive inpatient and day treatment program for children and adolescents with comorbid psychiatric and developmental issues. She is involved in multiple subspecialty clinics in the hospital, including the Prader Willi Multidisciplinary Clinic, the 22q11.2 Deletion Syndrome Clinic, and the Sie Center for Down Syndrome. She has also participated in national research studies looking at the effects of novel agents on the core behavioral phenotype of Fragile X Syndrome. In addition to managing her subspecialty clinic patients, Dr Sannar sees other outpatients for ongoing medication management. Dr Sannar brings her passion for serving special needs patients to her teaching of fellows and residents. She provides direct supervision to residents rotating through the NSC unit and lectures to general psychiatry residents, child and adolescent psychiatry fellows, and developmental pediatrics fellows.

Dr Sannar received her bachelor's degree in Women's Studies and Chemistry from Pomona College and her medical degree at the University of Chicago. She completed her residency and fellowship trainings at the University of Colorado School of Medicine.

Marissa Schiel, MD, PhD; Editor, Reviewer, Author

Marissa Schiel, MD, PhD is an assistant professor of psychiatry at the University of Colorado School of Medicine. Dr Schiel is an attending psychiatrist for the Eating Disorder Program at Children's Hospital Colorado. She also serves as the Medical Director of the Outpatient Psychiatry Clinic in the Pediatric Mental Health Institute. As part of her outpatient clinical responsibilities, she collaborates with Medical Day Treatment to provide psychiatric care for patients enrolled in their program. Dr Schiel is actively involved in teaching and committee membership for the child psychiatry residency program.

Dr Schiel received her bachelor's degrees in Biochemistry and Honors Biology from the University of Illinois, Urbana-Champaign and her doctoral degree in Biochemistry and medical degree from Indiana University. Dr Schiel completed her general psychiatry residency and her child psychiatry fellowship at the University of Colorado and served as a chief resident

Elizabeth Steinberg, PhD; Author

Elizabeth Steinberg, PhD is an assistant professor in the Department of Psychiatry at the University of Colorado School of Medicine. She is a pediatric psychologist for the Solid Organ Transplant program at Children's Hospital Colorado. Dr Steinberg conducts pre-transplant evaluations, consultations, and interventions for heart, liver, and kidney pediatric patients and families. Her research focuses on adherence interventions, assessment of adherence, and psychosocial aspects that impact coping with organ transplantation.

Dr Steinberg received her bachelor's degree in Psychology from Yale University, her master's degree in Clinical Psychology from Temple University, and her doctoral degree in Clinical Psychology, with an emphasis on Developmental Psychopathology, from Temple University. She completed her predoctoral internship in pediatric health psychology at Children's Hospital Colorado and her postdoctoral fellowship in pediatric psychology with an emphasis on pediatric solid organ transplant at Children's Hospital Colorado.

Ayelet Talmi, PhD; Reviewer

Ayelet Talmi, PhD is an associate professor of psychiatry and pediatrics at the University of Colorado School of Medicine and a pediatric psychologist at Children's Hospital Colorado. Dr Talmi is the Director of Integrated Behavioral Health at the Pediatric Mental Health Institute and serves as the Program Director of Project CLIMB, an integrated mental health and behavioral services program in a high-volume pediatric residency training clinic. Dr Talmi's positions include serving as the Associate Director of the Irving Harris Program in Child Development and Infant Mental Health (a fellowship training program in early childhood mental health), the Project Lead of the First 1,000 Days Initiative at Children's Hospital Colorado, and the Associate Director of the Center for Family and Infant Interaction (a transdisciplinary training center for professionals working with fragile infants and their families). Her primary clinical and research interests focus on building sustainable service delivery systems for children and families, integrating behavioral health services into primary care settings, and supporting young children with special health care needs and their families. Dr Talmi engages in workforce capacity building, training, technical assistance, and professional development efforts and has trained thousands of health, mental health, allied health, and community-based professionals. Dr Talmi is actively engaged in policy efforts around behavioral health integration in primary care settings, practice transformation, and payment reform. She is also involved in early childhood systems building efforts, advocacy, and policy in Colorado and nationally. Dr Talmi is a Graduate Zero To Three Leaders for the 21st Century Solnit Fellow and a Past President of the Colorado Association for Infant Mental Health.

Dr Talmi received her bachelor's degree in Psychology from Binghamton University and her doctoral degree in Child Clinical and Developmental Psychology from the University of Denver. She completed her internship at Children's Hospital Colorado and her postdoctoral fellowship in neurobehavioral development with the Developmental Psychobiology Research Group (DPRG) at the University of Colorado School of Medicine, Department of Psychiatry.

Eileen Twohy, PhD; Author

Eileen Twohy, PhD is an assistant professor of psychiatry at the University of Colorado School of Medicine and works as a pediatric psychologist at the Pediatric Mental Health Institute (PMHI) of Children's Hospital Colorado. Dr Twohy divides her time across the consultation/liaison service, intensive psychiatric services, and the outpatient clinic at PMHI. She enjoys providing consultation to medical teams as well as individual and group therapy to children, adolescents, and families presenting with a broad range of behavioral health concerns. Dr Twohy's role includes supervision and training of psychology interns and externs, medical students, and psychiatry fellows. Her interests include interdisciplinary treatment for children and adolescents with comorbid psychiatric and medical diagnoses, trauma-informed treatment, behavioral healthcare access for underserved populations, and transdiagnostic approaches to behavioral health.

Dr Twohy received her bachelor's degree in English from Grinnell College and her doctoral degree in Clinical Psychology from Catholic University in Washington, DC. She completed a predoctoral internship in pediatric psychology at Children's Hospital Los Angeles/University of Southern California, University Center for Excellence in Developmental Disabilities (UCEDD) and a postdoctoral fellowship in outpatient psychology at Children's Hospital Colorado.

Peng-Peng Wei, MD; Author

Peng-Peng Wei, MD is a resident physician in emergency medicine at New York-Presbyterian University Hospital of Columbia and Cornell. Dr Wei completed the work reflected in the paper published in this issue of the *Colorado Journal of Psychiatry and Psychology* as a medical student while part of the University of Colorado School of Medicine Research Track.

Dr Wei received her bachelor's degree in Molecular and Cell Biology and Psychology from the University of California, Berkeley and her medical degree from the University of Colorado.

Jason Williams, PsyD, MSEd; Author

Jason Williams, PsyD, MSEd is an associate professor of psychiatry at the University of Colorado School of Medicine and serves as Clinical Director and Director Quality and Safety in the Pediatric Mental Health Institute at the Children's Hospital Colorado. Dr Williams has an interest in the development of innovative teaching methodologies in inter-professional teams. Clinically, his interests lie in the use of technology both for clinical outcomes and in the development of transdiagnostic service delivery. He enjoys working with children and families clinically where he focuses on people with impulse control disorders.

Dr Williams is the past president of the Colorado Psychological Association and the past Chair of the Association of Predoctoral and Postdoctoral Internship Centers (APPIC); he is currently the Chair of the Council of Chairs of Training Councils (CCTC).

Dr Williams received his master's degree in Education from the University of Southern California and his doctoral degree from the California School of Professional Psychology in Los Angeles, California. He completed an internship and postdoctoral training program at the Children's Hospital in Los Angeles, where he worked for 12 years prior to returning home to Colorado.

Acknowledgements

Peer review is the major method for assuring high-quality scholarship in academic medicine. A knowledgeable and thoughtful peer review makes the papers she reviews better. We acknowledge the important contributions of our colleagues who served as peer reviewers for this issue of the *Colorado Journal of Psychiatry and Psychology*.

- Emily Edlynn
- Robert Freedman
- Jennifer Hagman
- Benjamin Mullin
- Doug Novins
- Philip O'Donnell
- Marissa Schiel
- Ayelet Talmi

Dedication

This issue is dedicated to the memory of Professor Randy Ross, who passed away as this issue was coming to press. Randy was an intellectual leader of our extensive developmental research portfolio at the University of Colorado and a highly respected scientist. Randy's work in translational neuroscience and his extensive knowledge of child development has led to innovative approaches to preventing the development of severe mental illness. He came to Colorado to train in our postdoctoral fellowship in developmental psychobiology, a program that he eventually would lead until his death. A highly sought after teacher and mentor, Randy was particularly talented at helping all of us to see our work from different perspectives, enabling us to do more rigorous and informative research. As Chair of the Department of Psychiatry's Promotions Committee, Randy immediately saw the value of this *Journal* for advancing the scholarship of our faculty. Indeed, Randy served as senior author for 2 papers in this issue of the *Journal*, underscoring his scientific accomplishments, mentorship, and dedication to our faculty and trainees. We treasure his legacy even as we struggle with coming to terms with our loss.

About the University of Colorado School of Medicine Department of Psychiatry

The University of Colorado School of Medicine is ranked in the top 10 by U.S. News & World Report in multiple medical specialties. Located on the Anschutz Medical Campus in Aurora, Colorado, the School of Medicine shares its campus with Children's Hospital Colorado and University of Colorado Health. The Department of Psychiatry provides clinical services through the Addiction Treatment Services, Children's Hospital Colorado, University of Colorado Hospital, and in conjunction with Denver Health Medical Center and the Denver Veterans Administration Hospital. The Department of Psychiatry training programs encompass a full spectrum of educational levels (from medical student and residency education through postdoctoral fellowships) and mental health disciplines (eg, psychology, psychiatry, social work, and nursing), and are widely recognized for their consistent high quality.

With over 167 full-time and 366 volunteer faculty members, the Department of Psychiatry is one of the largest in the United States. Its residency program also ranks among the largest programs, with 45 residents and over a dozen fellows. Many of our faculty have positions of leadership in national organizations, including the American Psychiatric Association, the American Psychological Association, and the American Academy of Child and Adolescent Psychiatry.

In terms of research, the Department of Psychiatry regularly ranks as one of the top 3 on the University of Colorado Anschutz Medical Campus, and was recently ranked 13th in the nation for research funding. It is also one of the strongest centers in the Veteran's Administration for funding in mental health research. The breadth and depth of scientific accomplishments span the neurosciences, developmental neurobiology, addictions, infant development, child and adolescent psychiatry, behavioral immunology, schizophrenia, depression, transcultural, and public psychiatry.

Recent research awards, investments in clinical services, and teaching by both our affiliated institutions and the philanthropic community have strengthened and enlarged our existing programs as we continue our commitment to a biopsychosocial model, medical and psychiatric education, an interdisciplinary research approach, and the provision of clinical services.

About the Division of Child and Adolescent Psychiatry

As one of the oldest and most-respected academic programs in children's mental health in the nation, the Division of Child and Adolescent Psychiatry supports a wide range of clinical, teaching, and research programs. The Division is particularly well-known for advancing the science and practice of children's mental health in the areas of addictions, anxiety, autism spectrum disorders, underserved populations, eating disorders, integrated care, psychosis and early-onset schizophrenia, psychosomatic medicine, stress and trauma, and telemental health.

The Division of Child and Adolescent Psychiatry combined efforts with Children's Hospital Colorado in 2002 to develop what is now the Pediatric Mental Health Institute. Children's Hospital Colorado sees, treats, and heals more children than any other hospital in the region, providing integrated pediatric health care services at the Anschutz Medical Campus as well as 16 other locations along Colorado's Front Range. The hospital is nationally ranked as a leader in pediatric care, consistently recognized by U.S. News & World Report as one of the top 10 children's hospitals in the nation.

The Pediatric Mental Health Institute provides a complete continuum of psychiatric services, including outpatient, emergency, partial hospitalization, and inpatient services with an emphasis on developing coordinated systems within the hospital as well as collaborating with other agencies and providers. Our interdisciplinary faculty and staff includes psychiatrists, psychologists, social workers, and nurses. The institute is in the midst of a major expansion that is touching all levels of clinical care, teaching, research, and scholarship, assuring its continued place as one of the nation's leading centers for children's mental health.

Department of Psychiatry | School of Medicine | University of Colorado

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