best” seems to demand a certain qualification: is the “best” the most interesting, most surprising, most educational, most important, most provocative, most enjoyable? How to choose? We are hardly unbiased and can admit to a special affection for the ones that we and the authors worked hardest on, hammering version after version into shape. Acknowledging these biases, here are the 2018 articles that we think deserve your attention or at least a second read.

Ongoing Charge to Advance Science in Support of Improving Clinical Care

Over the last year, the *Journal* has continued to welcome the opportunity to publish quality research papers that inform and enhance the provision of clinical care. In this context, we have had the privilege of publishing excellent papers on the management of aggression, attention-deficit/hyperactivity disorder (ADHD), and anxiety. One exemplar of this important work is represented in the article “Results From the Child/Adolescent Anxiety Extended Long-term Study (CAMELS): Primary Anxiety Outcomes.”[1](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib1) This article provides longitudinal data on the status of youth who participated in the multi-site Child/Adolescent Anxiety Multimodal Study (CAMS), providing unique insight into the longer-term needs of these youth. Predominantly cross-sectional data using a one-time postintervention assessment suggest that cognitive-behavioral therapy is associated with symptom remission for most youth. Although this is a heartening finding, the data from this longitudinal, multi-evaluation study provide a more sober assessment of treatment response in that only 22% of CAMS participants were “anxiety free” over the follow-up period whereas other participants had patterns of relapse or chronic illness. As emphasized by the investigators, data on long-term outcomes provide families with a more accurate sense of what to expect over time, as well as informing relapse prevention and treatment enhancement strategies. Study design included careful attention to identification of predictors of treatment response, underscoring that initial treatment response (across all treatment conditions), as well as younger age at first treatment, male gender, family support, and fewer negative life events were associated with stable remission. In sum, this study adds new depth to our understanding of childhood anxiety, emphasizes the need for ongoing effort to strengthen our treatment strategies, and provides some initial road signs to guide the way.

Another excellent example is provided by the meta-analysis by Strawn and collegues.[2](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib2) When we discuss with clinical colleagues the results of meta-analyses comparing a certain treatment to a passive control (eg, placebo), their usual comment is something like “We didn’t need another meta-analysis like this; we already know that this treatment is working for our patients.” We are confident that this is not the case for the meta-analysis by Strawn *et al.*, addressing very relevant, yet unanswered questions on the pharmacological treatment of anxiety disorders in children and adolescents. By pooling data from 9 trials (encompassing 1,673 youth), the authors found that: (1) clinically significant effect emerged by week 6; (2) compared to SNRIs, SSRIs were associated with a significantly greater improvement by the second week of treatment, which remained statistically significant through week 12; and (3) although improvement occurred earlier with high doses compared to low doses of SSRIs, the dose did not have any significant impact on the overall response trajectory. Along with the implementation of advanced meta-analytic methods, a strength of this paper is its focus on the difference between statistically and clinically relevant results, which unfortunately has been overlooked in several previous meta-analyses in the field. Overall, the work by Strawn *et al.* provided methodologically sound, invaluable evidence to guide the daily clinical decision making when using antidepressants for anxiety disorders in youth. We look forward to the implementation of a similar meta-analytic approach to address clinically relevant questions on the treatment of other child and adolescent psychiatric disorders.

**Samuele Cortese**

**Elizabeth A. McCauley**

From Clinical Practice and the Communities We Serve

When reflecting on a decision for this year’s “best” among the *Journal*’s clinically focused content, two articles came to mind that offer a dialectic definition of what the clinical content of the *Journal* can do. Turban and Keuroghlian’s Clinical Perspectives article on “Dynamic Gender Presentations: Understanding Transition and “De-Transition” Among Transgender Youth”[3](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib3) asked, and tentatively but optimistically answered, a question that many clinicians have been asking but may have been afraid to ask. The widespread desire in our field to approach gender fluidity in a supportive way can push aside questions of doubt and ambiguities, making certain questions or possibilities hard to countenance. On the other hand, Rappard and colleagues’ “Slowly Progressive Psychiatric Symptoms: Think Metachromatic Leukodystrophy”[4](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib4) does quite the opposite: it is asking and answering a question that probably very few of us are thinking.

As we continue to develop the clinical content of the *Journal*, we look for papers that ask and then offer at least a preliminary answer to the truly tough questions we face in clinical practice, including those questions we are afraid to ask and the ones we aren’t even thinking of asking.

As always, our portfolio of epidemiological and services research papers was filled with many outstanding contributions. Our choices for the best of 2018 focused on two issues critical to our field: gun violence, and screening for mental health problems in primary care settings.

To reduce gun violence, the American Public Health Association recommends a multi-pronged approach, including more robust controls on the purchase of and access to firearms, the development and deployment of gun safety technologies, better access to mental health services, enhanced surveillance of gun violence, and school- and community-based prevention programs.[5](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib5) For such programs to be well designed and successful, it is critical that we better understand the factors that predict participation in gun violence in a group particularly vulnerable to such behavior—youths with a history of criminal offending. Using data from 1,170 male juvenile offenders from diverse backgrounds who were followed for up to 7 years, Beardslee *et al.*[6](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib6) found that these youths were 40% more likely to carry a gun after they had been exposed to gun violence, but not other types of violence. The authors rightly argue for the importance of developing interventions for such youths to address their reactions to experiencing gun violence, but their findings also underscore how important a multi-pronged approach is, as preventing a single episode of gun violence could help reduce the cascading effect of exposure to gun violence.

It is commonly—and persuasively—argued that pediatric primary care providers should play a central role in addressing our nation’s crisis in children’s mental health.[7](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib7) But how? The recently revised Guidelines for Adolescent Depression in Primary Care (GLAD-PC) outline recommendations for strengthening pediatric primary care management of adolescent depression.[8](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib8) A key component of these recommendations is the provision of effective screening for mental health problems in primary care. Unfortunately, as the authors of GLAD-PC note, screening generates a significant number of false positives and negatives. Misidentifying youth as needing or not needing treatment not only exposes youth to the risks of over- and undertreatment, but imposes a burden on a limited service. One of the major challenges in developing more effective screening tools is that their performance is sensitive to the prevalence of mental health problems in a given population. More specifically, the accuracy of the screeners is reduced when the “base rate” of mental health problems is low, as is the case in many pediatric primary care settings. Young and Takala test a potential solution to this challenge—the sequential use of two different screening measures.[9](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib9) Because those children who screen positive on an initial measure are far more likely than those who screen negative to have a mental health problem, the next screener is working from a higher base rate, reducing false positives (and false negatives) after the completion of a second screener. By conducting a series of Monte Carlo simulations with three commonly used screening measures, the authors demonstrate that sequential screening results in more accurate identification of children in need of mental health services, although the best combination of screening measures varied depending upon the base rate of mental health problems in a given practice. Although there are certainly logistical issues in performing sequential screening in pediatric primary care settings, these are likely more than counterbalanced by the reduced cost of unnecessary assessments and referrals to an overburdened children’s mental health system.

**Schuyler W. Henderson**

**Douglas K. Novins**

Insights From Neuroimaging: Early Alcohol Use in TAOS Youth

In the August 2018 issue, Elsayed and colleagues[10](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib10) published the paper “Trajectories of Alcohol Initiation and Use During Adolescence and the Role of Stress and Amygdala Reactivity,” which evaluated the early neurobiological antecedents of alcohol use in 330 adolescents subsampled from 1089 youth participating in the Teen Alcohol Outcomes Study (TAOS; not the city). The participants were subsampled based on being at either high (n = 166) or low (n = 164) risk for depression at intake and had a mean age and follow-up period of approximately 13.5 and 4 years, respectively. The rationale for separating the youth based on risk for depression was that although historically it was thought that externalizing symptoms were most related to emerging alcohol use disorder (AUD), emerging evidence supports depression and depressive symptoms being commonly associated with AUD. Children with a psychiatric diagnosis at intake, except for anxiety in the group at high risk for depression) were excluded. The authors’ hypothesis was that greater alcohol use would be associated with a family history of depression, increased stress, increased threat-related amygdala activity, and decreased reward-related activity in the ventral striatum.

The authors used growth mixture models to identify 2 separate groups, one consisting of 32 individuals with early-onset alcohol use and the second with 298 either late initiators or abstainers. The authors attempted to apply a model with three classes; however, three different statistical tests all supported a two-class model that separated early-onset alcohol use from the other class. Early alcohol consumption was, not surprisingly, associated with developing an AUD, but also individuals with earlier-onset alcohol consumption showed greater amygdala activity to fearful facial expressions using task-related functional magnetic resonance imaging (fMRI). The early-onset alcohol group also experienced greater levels of stress but did not show decreased activity in the ventral striatum. Thus, factors that are also associated with depression and anxiety, including overreactivity of the amygdala and higher levels of stress, were associated with early and higher rates of alcohol consumption. However, the authors do not comment on whether the early-onset alcohol group was in the high- or low-depression group; thus there remains the question of reverse causality.

This study is of interest because of the early identification of neurobiological concomitants of early alcohol use in a longitudinal study. The sample size of 330 individuals is respectable for a neuroimaging study, and the ability to determine an early-onset group of early-onset alcohol consumption will be beneficial to determine early markers of at-risk alcohol use and to potentially direct interventions to normalize amygdala activity, given the inherent plasticity of the developing brain. However, as the participants underwent imaging at the second time point, it is unclear whether the amygdala activity differences predate alcohol consumption or whether they are a result of early alcohol consumption.

Higher levels of stress and increased amygdala activity, especially related to signals of threat, are associated with earlier initiation of alcohol use in youth. Determining putative risk and resilience factors for early-alcohol initiation is needed, given the major problems associated with alcohol abuse and dependence. Although not studied in this paper, the early identification of children with both higher levels of stress and depressive symptoms may curb the early initiation of alcohol use.

Childhood Adverse Experiences, Brain Connectivity, and Externalizing Psychopathology

The second article that we selected as representing the “best” of neuroimaging in 2018 was a paper published in the March issue of *JAACAP* entitled “Early Childhood Adverse Experiences, Inferior Frontal Gyrus Connectivity, and the Trajectory of Externalizing Psychopathology” by Barch and colleagues.[11](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib11) The authors were interested in testing the hypothesis that early adverse childhood experiences (ACEs) would influence child externalizing behavioral outcomes via an impact on the inferior frontal gyrus (IFG) brain connectivity (known to influence impulsive/risk-taking behavior). To test this hypothesis, they leveraged the data from a well-designed, 11-year longitudinal study with a large sample size. The authors collected data on ACEs. They had three waves of imaging data across childhood and adolescence, and they had phenotypic information from each wave regarding externalizing (and internalizing) psychopathology so that they could assess various trajectories and various influences on outcomes over time.

Notably, the authors report several important findings. First, ACEs did predict functional connectivity in the brain in the IFG bilaterally. The authors also found, using multi-level statistical modeling across all waves, that an increased number of ACEs predicted more internalizing and externalizing symptoms. Yet, altered IFG connectivity predicted only externalizing (not internalizing) symptoms in middle childhood and adolescence, and this relationship was maintained across all waves of assessment. Unfortunately, the analyses in this study did not demonstrate that IFG connectivity mediated the relationship between ACEs and externalizing symptoms. However, the authors conclude that the brain connectivity of the IFG may play a central role in the relationship between ACEs and externalizing behaviors. Therefore, this study gives us some insight into the neural mechanisms by which ACEs may lead to negative behavioral outcomes.

Despite this wonderful work, it remains clear that further efforts are needed to elucidate whether these associations are a direct effect of ACEs or whether ACEs are markers of other factors (environmental/genetic) that may have an influence on brain and behavior.

This article achieves the “best” status for important reasons. First, it is a study that enrolled a very large sample size of depressed preschoolers (n = 211) in the initial wave; second, it is a longitudinal study across 11 years that includes 3 time points that include both emotional and behavioral assessments and imaging acquisition. This is by far one of the best imaging studies we have published this year, for the above reasons. Kudos to the authors for exemplary work!

**Jean A. Frazier**

**Tonya J.H. White**

So Complex…and Yet So Simple: Our Picks for Best of 2018

In the two articles that we chose as our “best of 2018” you'll find complicated research methods that provide important, basic principles directly applicable to clinical practice. There is an elegance in the methods and tangible clinical take-home messages that feed both our inner scientist and our inner clinician.

***The Impact of Antidepressant Dose and Class on Treatment Response in Pediatric Anxiety Disorders: A Meta-Analysis.***[***2***](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239#bib2) This work is at once very precise in its methodology while at the same time being exceedingly practical. Strawn and colleagues, noting the adult literature demonstrating that selective serotonin reuptake inhibitor (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may demonstrate early response to treatment for anxiety and obsessive-compulsive disorder (OCD), sought to examine this issue in children. Using complex, yet powerful, Bayesian meta-analytic techniques, the authors integrated 9 double-blind randomized controlled trials, which enrolled 1,805 children, and directly compared 8 different antidepressants to placebo. They concurrently investigated the role of the dose of the antidepressants, the time course of response, and differences between SSRIs and SNRIs in the treatment of childhood anxiety. Surprisingly, the time series models they created demonstrated that anxiety symptoms statistically separated from placebo as early as 2 weeks, with clinically significant separation by 6 weeks. SSRIs showed a larger response than SNRIs. There was little difference for high and low doses of SSRIs. Taken overall, these results suggest that, given our current evidence base, SSRI treatment shows a quick response for anxiety, even at low doses. This work, elegantly performed using state-of-the art meta-analytic techniques, allowed the researchers to recommend the use of SSRIs as first-line treatment for childhood anxiety. Although additional research is needed, the data are promising and important as we discuss with our patients and their families the benefits and risks associated with pharmacotherapy for pediatric anxiety. As good reviews go, the authors also provided putative biological mechanisms for the differences between SSRIs and SNRIs. Want to know those mechanisms? Check out the paper. Not only did we think it was one of the best of 2018, our editorial colleagues Samuele Cortese and Elizabeth McCauley heartily agreed!

***Parenting Is an Environmental Predictor of Callous-Unemotional Traits and Aggression:A Monozygotic Twin Differences Study.******[12](https://www-sciencedirect-com.ezproxy.med.nyu.edu/science/article/pii/S0890856718320239%22%20%5Cl%20%22bib12)*** Nature versus nurture? At this point, we all recognize that this is a false dichotomy. Since the description of gene-by-environment interactions and correlations took the world by storm in the early 1990s, there has been a movement toward considering genes and environment concurrently, and perhaps equally important, interactively. A particularly challenging area for this debate is in relation to early antisocial behavior, given that current treatments of CU and antisocial behavior fall far short of basic levels of effectiveness. Twin studies have shown that callous-unemotional traits are highly heritable. Because of this, and the gene−environment correlation of a child at risk for CU traits being raised by a CU parent, there has been a sense of predetermination of the child with CU traits—who may evoke more harsh parenting and lower warmth, creating a powerful negative spiral of risk. This spiral, however, has been challenged (at least to some extent) by adoption studies demonstrating that low parental warmth in adoptive parents may further elevate risk; however, these studies do not fully address the questions of shared genetics and shared environment that appear particularly challenging for CU. In this work, Waller and colleagues use a large cohort of monozygotic twins to examine directly this cycle of genetic risk and parenting. Using this unique study design, they used one twin as the genetic control for the other, thereby isolating the role of parental harshness and low warmth from the genetic effects. Their results were striking. Parental harshness was associated with both child aggression and CU traits. However, lower parental warmth was uniquely related to child CU traits. Again, using a relatively complicated design, the result is tantalizingly simple. CU traits, despite decades of concern, are not immutable. There are environmental factors, specifically parental warmth, that likely modify risk trajectories. Beyond the direct influence of parental warmth and harsh parenting another finding also arose—one with clinical relevance. The impact of harsh parenting on aggression was exacerbated in low-income families, indicating that for low-income families, many of whom we treat, directly addressing harsh parenting practices, including corporal punishment, is likely crucial to decrease aggression. Taking these findings together, this study highlights the relevance of family/parenting interventions for children with CU traits and that these interventions have the potential to reduce their “highly heritable” predisposition to aggression.

**Robert R. Althoff**

**Stacy S. Drury**