STUDY PROTOCOL AND METHODS ADVANCEMENT

Cross-Cultural Consortium on Irritability (C3I): An International Network for Research on Cultural Similarities and Differences in Irritability

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Objective: Irritability is among the top reasons for youth mental health referrals worldwide. Cultural factors may affect how irritability manifests and develops; how it is experienced by youth and responded to by their caregivers; and how it is treated. However, the influences of cultural context on irritability have received little systematic investigation.

Method: The Cross-Cultural Consortium on Irritability (C3I; https://m.yale.edu/c3i) is an international research network created to increase the limited evidence base on cross-cultural similarities and differences in irritability. By bringing together researchers worldwide, C3I provides an innovative and collaborative approach to address unmet needs and to explore novel research questions regarding cultural variation in irritability. In addition, combining resources and data around the globe helps to produce robust, reproducible, and generalizable results using large mega-data. One important initiative involves pooling existing datasets to support manuscript collaborations. The first 3 such projects focus on cross-cultural comparisons of the following irritability-related topics: boundaries of normative behavior; association with suicidality and self-harm; and informant effects. Another ongoing effort involves conceptualization of irritability across cultures. Other efforts include promoting projects of primary data collection using qualitative and quantitative methods, harmonization across measures, and facilitating/supporting community-based participatory research and engagement.

Discussion: C3I is an innovative, collaborative research structure to build a robust, reproducible, and generalizable evidence base on irritability and its characteristics, including sociocultural influences. This evidence base will facilitate recognition and assessment of irritability and, ultimately, inform development of effective, culturally informed prevention and intervention to benefit the largest possible number of youth and their families.

Plain language summary: This article describes the Cross-Cultural Consortium on Irritability (C3I), an international network aimed at understanding how culture shapes the presentation, experience, response to, and treatment of irritability in youth. By exploring these cultural influences, C3I seeks to improve recognition, assessment, and development of effective, culturally sensitive prevention and intervention strategies to benefit the largest possible number of youth and their families worldwide.

Key words: irritability; cross-cultural research; culture; consortium; international network

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Irritability, which can be defined as "proneness to anger that may impair an individual's functioning,"[1] is one of the most common reasons for youth (ie, children and adolescents) being referred for mental health assessment and care.[2,3] Irritability in youth began to gain research attention in the early 1990s when chronic irritability in youth was viewed by some child psychiatrists as a developmental form of pediatric bipolar disorder.[4,5] A series of longitudinal, familial, behavioral, and pathophysiological studies since then have disputed this view.[4,5] Irritability has wide-reaching effects on youth and families, schools and communities, and the mental health care system. Critically, irritability in youth has been linked to a wide array of adverse outcomes, including suicidal ideation and behaviors,[6–8] depressive and anxiety disorders,[9–12] functional impairment at home, in school, and with peers,[9–13] and low income and educational attainment in adulthood.[10,12] Importantly, irritability is also a common presenting symptom across multiple disorders in adults and is associated with significant impairment across the lifespan; however, there is little research on adult irritability.[14]

Despite its high individual and public health impact in youth, no firmly established evidence-based interventions exist for irritability outside the context of autism spectrum disorders.[15] More recently, disruptive mood dysregulation disorder (DMDD), which specifically involves non-episodic irritability and frequent severe temper outbursts in children, was included in the *DSM-5* to facilitate both more research as well as diagnostic and treatment advances; however, research and clinical practice in DMDD are still in its early stages.[16] Given that irritability is a trans-diagnostic symptom that cannot clearly be attributed to a specific mental disorder, understanding it requires a broad, comprehensive approach. A critical barrier is the limited evidence base about the underlying biological, psychosocial, and environmental mechanisms of, and contributors to, irritability. Enhanced etiologic understanding of irritability can pinpoint actionable transdiagnostic targets to improve the identification, treatment, and prognosis of irritability, thus reducing the burden on individuals, their families, and educational and mental health care systems.

Environmental influences crucially contribute to individual differences in irritability.[17] More broadly, studies show that perception and experience of emotion, including anger, are not universal across cultures.[18] For example, Japanese university students rate facial expressions as less intense than do their American peers.[19] Similarly, the experience of emotion can vary by culture.[20,21] Americans tend to experience emotion as subjective feelings and internal mental states, whereas the Hadza, a community of hunter-gatherers in Tanzania, describe emotion as external experience tied to the physical and social context of an event and their associated bodily sensations.[21]

Sociocultural factors are likely to be among the significant environmental inputs systematically shaping how irritability presents, how it is experienced by youth and caregivers, and how caregivers respond to it. Decades of research demonstrate that parents, caregivers, and others in the youth's environment are key influences on how the youth understands, experiences, expresses, and regulates emotions.[22–24] How emotions are taught and managed (ie, emotion socialization, as well as norms regarding emotional expression and competency) vary across cultures.[25] As an example, a study found that mothers from the United States indicated aggressive and disruptive behaviors as the most salient child misbehaviors, whereas mothers from mainland China emphasized cognitive and motivational difficulties.[26] Moreover, American mothers were more likely than Chinese mothers to attribute child misbehaviors to momentary negative internal states (eg, "s/he was frustrated"), followed by immature development. In contrast, Chinese mothers attributed child misbehaviors primarily to social influences, followed by temperament.[26] There is also robust evidence for cross-cultural variability in mean levels of parent-, youth-, and teacher-rated child emotional and behavioral problems.[27,28] This research indicates that, even when symptom measures display configural and metric invariance across different cultural groups, the score range representing typical (vs atypical) levels of irritability often varies from one cultural group to another.[27,28] These variations likely reflect cross-cultural differences in how youth emotional and behavioral problems manifest and are perceived; thus, it has been recommended that clinicians use culturally specific normative data[27] and/or cross-culturally validated measures,[28] whenever possible.

Problematically, most literature on irritability relies on data from Western, Anglophone, high-income countries (HICs; eg, United States or United Kingdom). However, many methods and paradigms used to study the pathophysiology of irritability show variability across cultures.[29] Studies from low- and middle-income countries (LMICs), and from subcultures within both HICs and LMICs, are imperative to build an evidence base that accurately reflects the populations worldwide. This evidence base should include multiple languages and cultures, including those in the Global South, conducted by investigators from various cultures and backgrounds.

Focusing on irritability specifically, cross-cultural research should address similarities and differences in its phenomenology, developmental expression, measurement, and correlates, as well as responses by caregivers, teachers, health care providers, and others.[1] A few emerging studies provide the first empirical data on cultural similarities and differences in irritability. One recent international study that included an online sample of adults from 10 countries (Australia, China, India, Ireland, Malaysia, New Zealand, Singapore, South Africa, United Kingdom, and United States) found that irritability was common across countries without significant cultural differences in its frequency.[30] However, there were cultural differences in the duration of irritability.[30] To our knowledge, there is only one published cross-cultural study of irritability in youth. It was conducted by investigators residing in 9 countries (China, Colombia, Italy, Jordan, Kenya, Philippines, Sweden, Thailand, and United States) spanning 12 cultural groups.[31] Across cultures, the investigators found similar processes linking adolescent irritability with parental irritability and self-efficacy in anger regulation.[31] A recent investigation by several members of C3I in a large adolescent sample (N = 56,324) from 9 countries (Bulgaria, Georgia, China [Hong Kong], Ireland, Mexico, Panama, Serbia, Spain, and the United Arab Emirates) also found no substantial variation in irritability frequency.[32] However, there were differences

across countries in associations between irritability and life satisfaction and bullying.[32] Taken together, these findings underscore the need for more cross-cultural research on pediatric irritability to better understand sociocultural influences on irritability and its characteristics and to facilitate the recognition and assessment of irritability in multiple groups and countries. Ultimately, this effort will help to address health disparities by developing effective, tailored prevention and interventions with careful considerations of sociocultural factors. Toward that goal, the Cross-Cultural Consortium on Irritability (C3I) was established.

Of note, although data are relatively scarce on adult irritability compared to the youth literature, C3I is interested in both youth and adult populations. Moreover, it is important to highlight that C3I's focus is not just on environmental and cultural influences on irritability. Given that the mechanisms and etiology of irritability are likely multi-determined, C3I also aims to leverage its infrastructure to increase the evidence base regarding the biological underpinnings of irritability (eg, genetics, neural mechanisms) and their interplay with environmental factors (eg, genetic and environmental correlations and interactions through parent–child and peer relationships and/or cultures). As a further avenue, data pooling on research regarding diagnostic and intervention approaches may also be included as part of the Consortium's effort and activities.

METHOD

A Brief History of C3I

C3I was launched in May 2022, following an initial concentrated effort to identify and contact international investigators working with a variety of populations. Since its inception, C3I has attracted 145 researchers from 29 countries (Figure 1 depicts the distribution of the countries from which Consortium members originate or where they reside). Approximately 40% of the members are from the United States (Figure 1). (For information about the Consortium including history, mission, participating members, and how to join, please visit the website at https://m.yale.edu/c3i.)

Initial Survey Findings

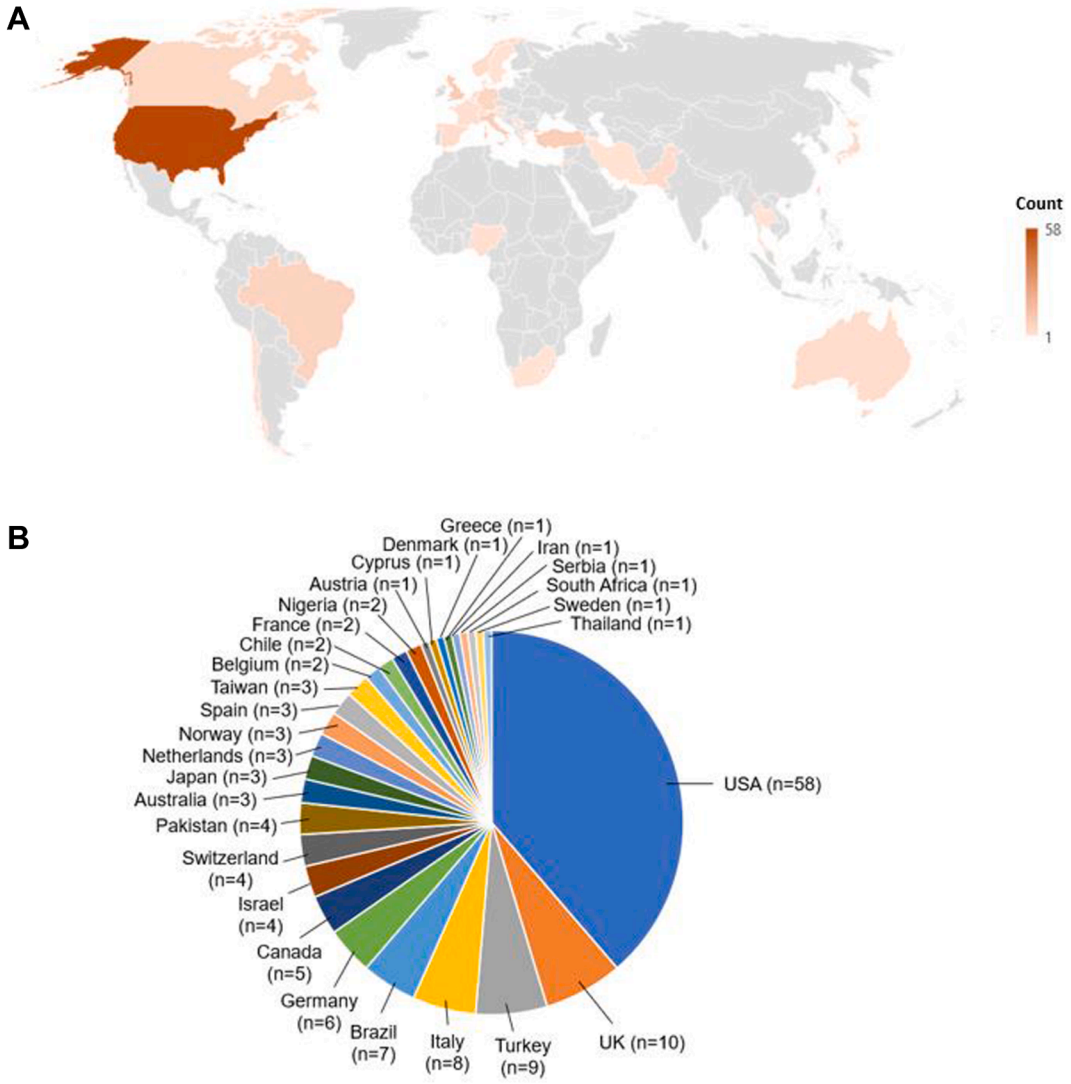
To engage Consortium members in planning future activities, a brief online survey (Supplement 1, available online) was sent to all members in September 2022. It asked about Consortium members' interest in participating in various activities and what they considered as the most pressing research questions. The response rate among the 95 members at the time was 71%, evidencing the collective enthusiasm for cross-cultural irritability research.

Of the respondents (n = 67), 34 expressed interest in sharing data; 11 indicated that they had longitudinal data to share, 13 had cross-sectional data, and 10 had both. Data covered birth to age 25 years (Figure 2 depicts the distribution of datasets among the 9 countries where they were collected). Among the 34 datasets, 22 were from the United States (~55% of the American data are from traditionally underserved groups), 3 each from Brazil and Canada, and 1 from each of the other 6 countries. Of these data, the most commonly examined constructs were irritability, followed by emotion (dys)regulation, reactive and proactive aggression, mood symptoms (depression, mania), and attention-deficit/hyperactivity disorder (ADHD) (Figure 3a). The most commonly used irritability measures were the Affective Reactivity Index (ARI),[33] followed by the Child Behavior Checklist (CBCL),[34] and the Kiddie-Schedule for Affective Disorders (KSADS)[35] (Figure 3b).

Members identified several pressing research themes to be addressed by C3I. One set of questions centered on cross-cultural variation in phenomenology, mechanisms, and outcomes, including the following: (1) conceptualization and definition of irritability and emotion dysregulation; (2) symptom presentation of irritability across developmental periods; (3) normative boundaries of irritability; (4) caregivers' and children's experiences and perception of irritability, including temper outburst triggers; (5) how parents respond to the child's irritability, including when and from whom parents seek help; (6) longitudinal outcomes of irritability, eg, suicidal behaviors, non-suicidal self-injury, depression; (7) risk and protective factors (eg, trauma exposure); and (8) comorbidity with other clinical problems and conditions (eg, ADHD, depression, posttraumatic stress disorder [PTSD], anxiety, stress, aggression, and disruptive behavior disorders).

Another set of research questions related to measurement. These research questions included the following: (1) cultural variation in the validity and reliability of extant irritability measures; (2) improvement of ambulatory measurement of irritability (eg, experience sampling methods); (3) multi-informant discrepancies in irritability ratings; (4) assessment tools for irritability across development, from childhood to adulthood; (5) harmonization of irritability measures in pooled samples; (6) use of measures specifically designed to assess irritability, rather than drawing irritability-related items from existing measures; (7) development of irritability instruments for use in multiple populations that are valid with respect to how irritability presents and is perceived and reported, using qualitative and quantitative methods.

FIGURE 1 Countries From Which Consortium Members (N = 145) Originate, in a World Map (A) and a Pie Chart (B)



A third pressing research priority noted by multiple respondents was the inclusion of more samples from various social, cultural, and economic backgrounds and environments within and across countries, especially participants from underrepresented rural communities.

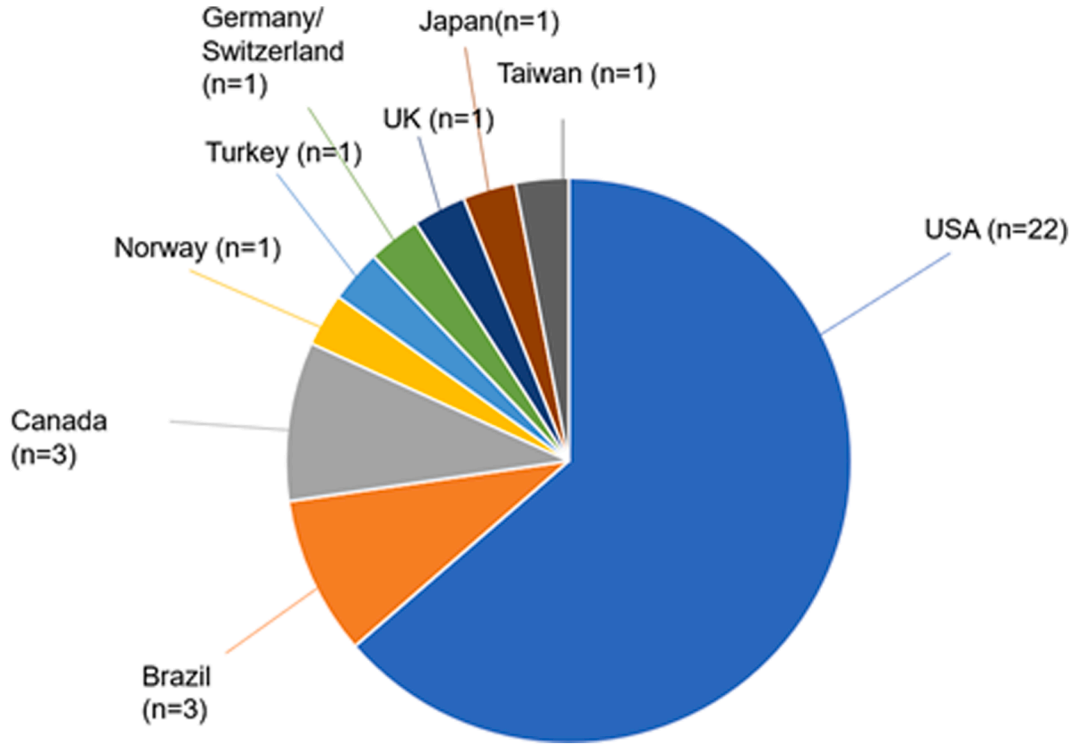
Mission and Goals

Based on the survey results and Steering Committee discussions (discussed below), participants decided to define C3I's mission as bringing together researchers and clinicians interested in studying variation and commonalities across cultures (both between and within countries) in the risk factors, correlates, assessment, experience, parental experience and responses to, outcomes and treatment of irritability, along with other relevant topics. The overarching goal of C3I is therefore to provide a collaborative structure for researchers interested in cross-cultural aspects of irritability.

Furthermore, the members of C3I state that the following values and principles will guide all of our activities.

- Open participation, transparency, integrity, and fairness
- High-quality scientific work
- Provision of training and mentorship opportunities to early career researchers
- Engagement of perspectives from community partners in the design, conduct, and dissemination of the research

FIGURE 2 Distribution of the Origin of Datasets (N = 34) That Consortium Members Indicated Interests in Sharing



- Following of open science practices (eg, material and data sharing; maintenance of public data repositories; preregistration of research projects).[36]

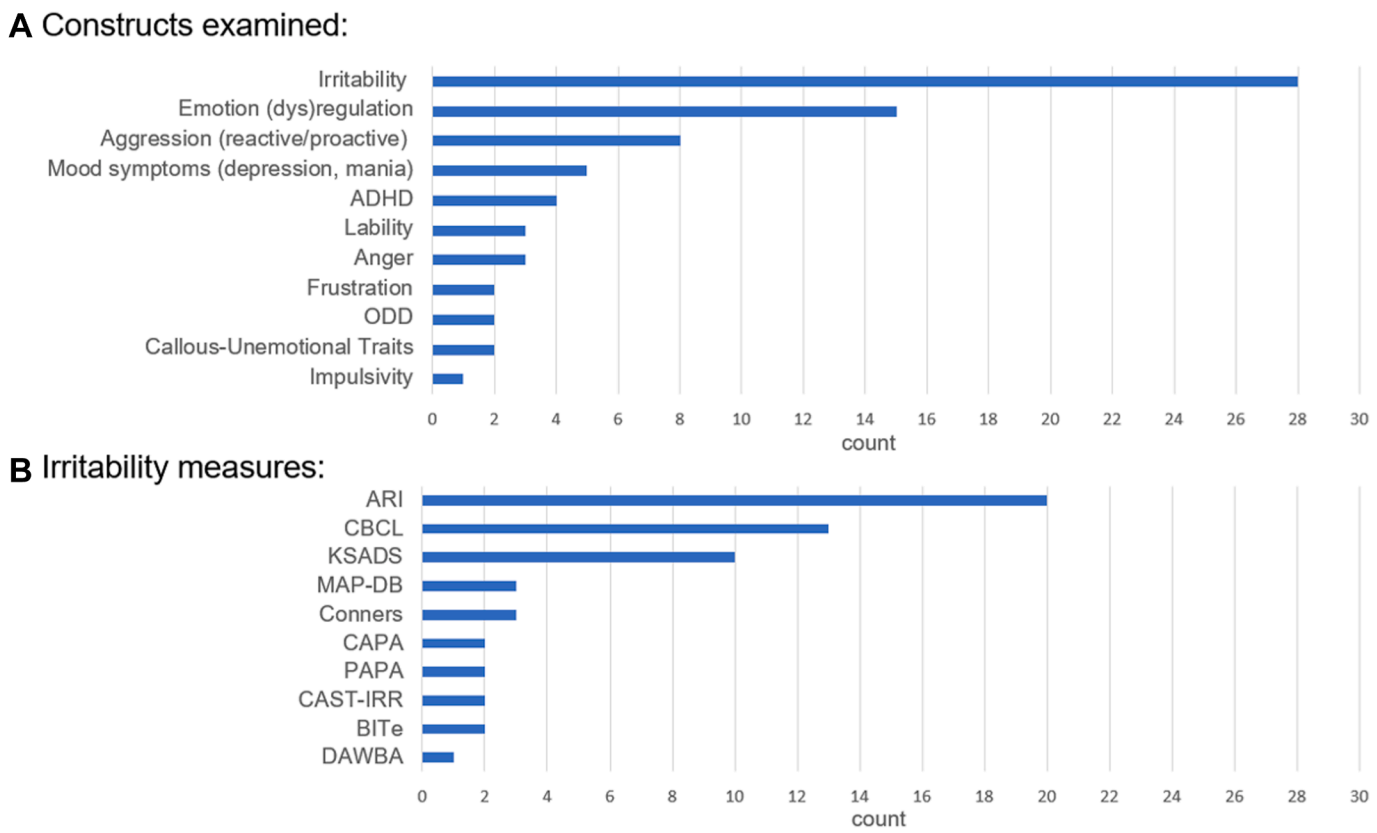
C3I's mission statement is available in Supplement 1, available online, and at https://m.yale.edu/cv6h.

Methodological Innovations and Considerations

As an international research network, the C3I takes an innovative, collaborative approach to advancing the currently limited knowledge base on cross-cultural similarities and differences in irritability. Global research collaborations are not novel. An International Study of Schizophrenia (IPSS) by the World Health Organization (WHO)[37] was first launched in 1960s. Many other international networks on psychiatric and mental health research were subsequently established, including the Psychiatric Genomics Consortium (PGC)[38] and the Hierarchical Taxonomy Of Psychopathology (HiTOP) Consortium.[39,40] Other initiatives aggregate neuroimaging data from laboratories around the world: for example, the Autism Brain Imaging Data Exchange (ABIDE)[41,42] and the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)[43] Consortium, the latter of which has an irritability working group. However, beyond the narrower focus of the ENIGMA irritability working group, the C3I is the first international research network centered specifically on irritability.

Importantly, there may or may not be meaningful cultural variability in irritability, and data from large samples with varied social, economic, ethnic, and cultural backgrounds are required to identify or to rule out such cultural variation. Whether findings point to universal patterns or cultural specificity, the generated knowledge will inform future research and clinical work around the globe. For example, the few cross-cultural studies on irritability reported no significant cultural differences in the mean levels of irritability.[30,32] However, these results were based on measures with unknown measurement equivalence across cultures. Language, cultural context, and ecological, convergent, and internal validity all contribute to the perception, experience, and expression of emotions.[44] Careful consideration of these factors and the use of more generalizable measures (including qualitative and language-free approaches) might reveal nuances in cross-cultural similarities and differences in irritability. Pooling resources and data from a wide variety of settings not only enables us to address questions related to culture but also improves the robustness, reproducibility, and generalizability of findings through large-scale mega-data.

FIGURE 3 Irritability-Related Constructs (A) and Measures (B) in the Datasets (N = 34) That Consortium Members Indicated Interest in Sharing



Note: *ADHD = attention-deficit/hyperactivity disorder; ARI = Affective Reactivity Index; BITe = Brief Irritability Test; CAPA = Child and Adolescent Psychiatric Assessment; CAST-IRR = Concise Associated Symptom Tracking—Irritability; CBCL = Child Behavior Checklist; DAWBA = Development and Well-Being Assessment; KSADS = Kiddie-Schedule for Affective Disorders; MAP-DB = Multidimensional Assessment of Preschool Disruptive Behavior; ODD = oppositional defiant disorder; PAPA = Preschool Age Psychiatric Assessment.*

One key initiative of C3I involves pooling existing datasets and using them to facilitate secondary analyses. It is expected that secondary analyses will yield publications that provide important knowledge to the scientific community. Importantly, these analyses will generate critical pilot data to demonstrate feasibility for grant applications. In line with our goals, C3I encourages investigators who are interested in studying cross-cultural differences and similarities in irritability-related topics but who do not yet have the resources to collect or access such data, including trainees and early-stage investigators or researchers from countries and institutions with limited means, to take advantage of these pooled datasets.

In addition to providing a framework for secondary analysis of existing datasets, C3I plans to develop research projects involving primary data collection. As described below, working groups around specific topics and meetings are focusing on designing projects and obtaining funding. Although the exact nature of these projects will depend on members' interests, we encourage the use of both qualitative and quantitative research methods.

Although many C3I initiatives and efforts have gained traction and generated substantial enthusiasm among researchers in the field of irritability and child mental health, forming and sustaining the Consortium is not without challenges. A major obstacle is that C3I is self-funded, relying on volunteer investigators' time and resources to support ongoing initiatives and activities. It has been difficult to identify and to obtain funding to support cross-cultural work on irritability. Another challenge is the variety of measures used to probe irritability in the existing studies and datasets. Rigorous data harmonization, which is underway, would be critical to meaningfully compare results across studies and datasets. Moreover, about 40% of the Consortium members are based in the United States. Identifying investigators from other countries and cultures has been challenging.

C3I Structure

The C3I consists of a Steering Committee and 5 working groups (Figure 4 depicts the current structure of C3I with brief descriptions of the primary function of each group).

Steering Committee

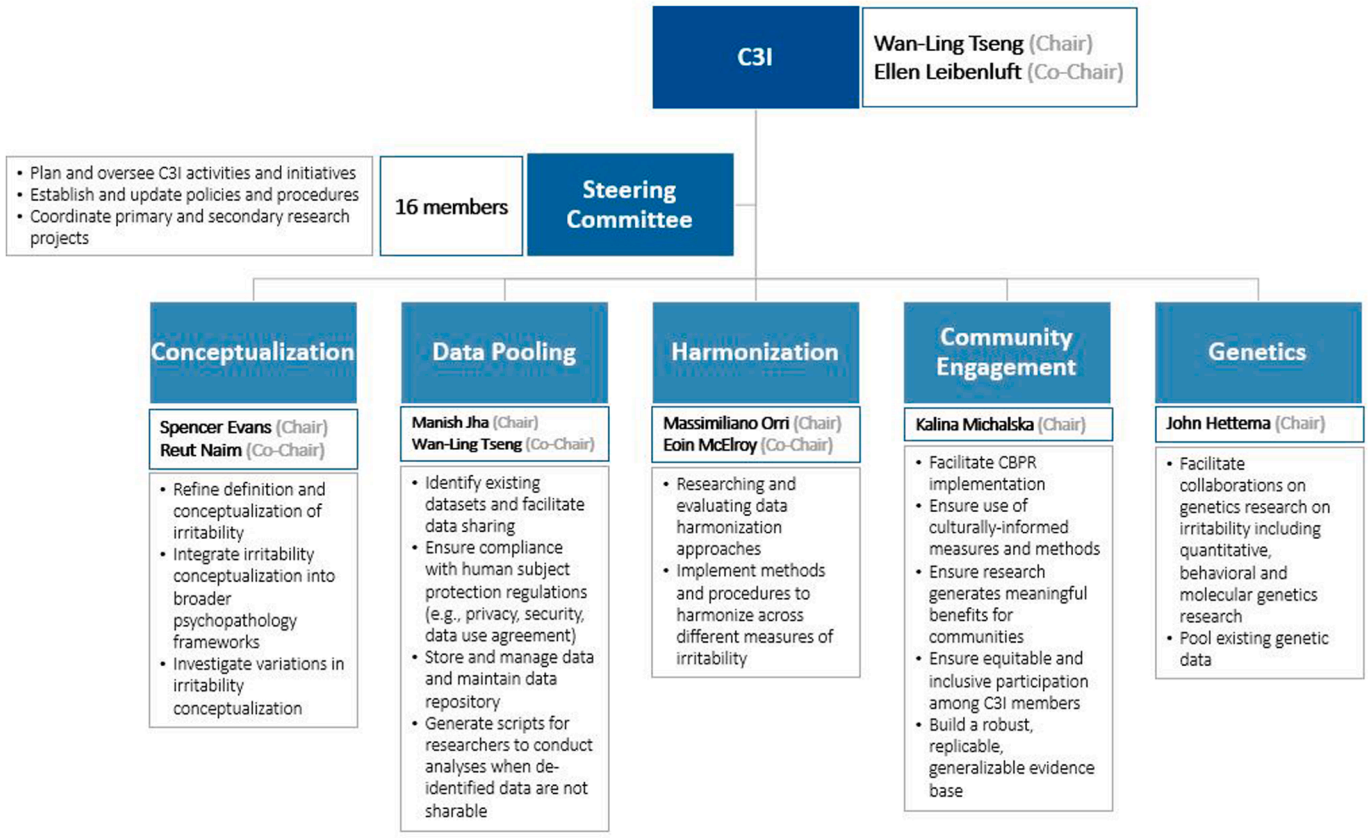
The C3I Steering Committee (SC) consists of Dr. Wan-Ling Tseng (C3I Chair), Dr. Ellen Leibenluft (C3I Co-Chair), and members from various countries of residence (Brazil, Canada, Germany, Israel, Spain, Taiwan, United States, United Kingdom, and Greece), educational level (MDs, PhDs, masters, predoctoral students), career stage (early-stage/junior and senior researchers), discipline (psychology, psychiatry, neuroscience, epidemiology, public health), and demographic groups (for a list of SC members, please see the C3I website). The SC was formed following an open call for participation. The SC plays a coordinating role in both primary and secondary research projects by reviewing and approving proposals. The review and approval process are designed to ensure that the projects of participating researchers are complementary and open to all Consortium members who wish to contribute. The SC also facilitates efficient communication within the C3I about ongoing projects. The SC has established publication guidelines to ensure consistency across projects (Supplement 1, available online, or C3I website).

The SC meets monthly to discuss ongoing efforts and activities (eg, data-pooling, manuscripts, projects), to identify opportunities for collaborative efforts, to establish and update policies and procedures, and to plan Consortium-wide virtual meetings to update members on activities and brainstorm ideas for future work.

Working Groups

The C3I has 5 working groups tasked with leading specific initiatives. These are as follows: (1) Conceptualization, (2) Data-Pooling, (3) Harmonization, (4) Community Engagement, and (5) Genetics (Figure 4). Below, we briefly describe each working group. We anticipate that additional working groups will be created by the SC based on the

FIGURE 4 C3I Current Structure and Primary Function of Each Group



Note: *C3I = Cross-Cultural Consortium on Irritability; CBPR = community-based participatory research.*

interests of members. In fact, an Artificial Intelligence and Treatment group is currently being formed.

Conceptualization (Chairs: Drs. Spencer Evans and Reut Naim). The goal of the Conceptualization Working Group is to facilitate progress in understanding irritability and integrating it into broader knowledge and frameworks of psychopathology. Such frameworks include the *DSM*,[45] *International Classification of Diseases* (*ICD*),[46] HiTOP,[39,40] Research Domain Criteria (RDoC),[47] and other atheoretical or theoretical models.[5,48–50] Much has been written about how irritability is transdiagnostic and linked to a variety of problems and disorders.[1] Although these properties say something about the ubiquity and clinical significance of irritability, they also show that it is nonspecific, heterogeneous, and poorly understood. New research on any topic must relate its findings to existing conceptual frameworks and bodies of evidence before it can lead to broad-based advances in science and practice. The Conceptualization Working Group seeks to address this need in the case of irritability—that is, to define how irritability "fits" within what is known about psychopathology more broadly. Specific goals are described in Figure 4. Planned activities include collecting survey data on the conceptualization of irritability in C3I members' cultural groups, leveraging existing datasets, and developing empirical and review papers. This could include investigating the internal state and experience and the external manifestations of anger and irritability, and how cultural factors influence these internal and external manifestations of anger and irritability as well as the impact of these manifestations on the individual's functioning. Ultimately, this work could serve as a springboard for collaborations and advances in how irritability is conceptualized, defined, measured, and managed in multiple settings.

Data-Pooling (Chairs: Drs. Manish Jha and Wan-Ling Tseng). The Data-Pooling Working Group is charged with tasks related to data sharing (Figure 4). We use the pooled datasets to address pressing research questions suggested by Consortium members. Below, in the Research Projects in Progress section, we describe 3 current projects that use these pooled datasets.

Harmonization (Chairs: Drs. Massimiliano Orri and Eoin McElroy). One of the main challenges in irritability studies concerns the multiple ways in which irritability is defined, operationalized, and measured across different research groups and laboratories. The Harmonization Working Group is tasked with harmonizing different measures and instruments used to assess irritability (Figure 4). Specifically, the working group is researching data harmonization approaches and will implement methods and procedures, such as natural language processing of questionnaire items and factor analytic tools. Work by the Harmonization group will eventually contribute to refining the definition and operationalization of irritability and deriving common, standardized measures across research groups and laboratories, thereby improving consistency in research findings.

Community Engagement (Chair: Dr. Kalina Michalska). Consortium members expressed considerable enthusiasm about community engagement and community-based participatory research (CBPR)—a collaborative approach that brings together researchers and community members to tackle issues that have impacts on community wellbeing. This approach emphasizes shared power, mutual respect, and the development of community–academic partnerships.[51] One of C3I's goals is to act as a catalyst for supporting members' community engagement efforts with considerations of issues regarding representation and positionality in cross-cultural research on irritability. Primary functions of the Community Engagement Working Group include facilitating the implementation of CBPR on irritability by involving children, adolescents, and families affected by irritability. These community members serve not just as participants, but as equal partners—helping to co-create the research of which they are a part, including study co-design, implementation, and dissemination. Other functions are outlined in Figure 4.

Genetics (Chair: Dr. John Hettema). The Genetics Working Group aims to facilitate close collaborations between Consortium members interested in understanding the genetic underpinnings of irritability by pooling existing genetic data and conducting genetic research to broaden the existing genetic database that is currently limited to a small subset of the world's populations. The research scope includes both quantitative, behavioral genetics research (ie, twin and adoption studies) and molecular genetics research (eg, genome-wide association as well as epigenetics and gene expression).

Research Projects in Progress

As described above, a major ongoing effort of the C3I is to pool existing datasets across research groups from various regions, cultures, and countries. We are using these datasets

to address pressing research questions suggested by Consortium members. Below, we describe 3 ongoing research projects that leverage the pooled datasets. Key information about the data and methods for each project is presented in Table 1. The following is a description of each project's background, rationale, and potential contribution to the field.

Norms and Empirical Thresholds of Pediatric Irritability Across Cultures. There has been progress in identifying the typical vs atypical boundary of irritability and deriving empirical thresholds of severe, impairing irritability.[52–54] Although there has been some research on how basic emotions including anger are similar or different across cultures,[18–20] the extent to which thresholds of normative vs clinically impairing irritability vary across cultures is unclear.[30] This project aims to address this gap by deriving norms and empirical clinical thresholds of irritability using pooled data from the C3I. Delineating the typical vs atypical boundary of irritability and establishing empirical thresholds of severe, impairing irritability across cultures are critical first steps toward a better understanding of cross-cultural similarities and differences in how irritability manifests, is perceived, and is experienced by caregivers and children. This work will lay the foundation for future research that is generalizable across multiple populations on the etiology, development, and mechanisms of severe, impairing irritability in children and adolescents, and will provide an important framework for the development of interventions that can benefit the maximal number of children.

Association Between Irritability and Suicide-Related Outcomes Across Cultures. Recent studies suggest a link between irritability and suicide-related outcomes, potentially identifying irritability as a promising transdiagnostic risk factor that can be used to predict suicide-related outcomes.[6,55] However, evidence remains limited and is based primarily on Western samples.[7] This project aims to address the gap in the literature by investigating associations between irritability and suicide-related outcomes, such as suicidal ideation, suicide attempt, and non-suicidal self-injury across a variety of populations. We will take an individual participant data meta-analytic approach that is flexible and allows us to use deidentified data directly shared with the C3I as well as summary statistics generated locally using a harmonized analysis protocol. This approach will enable us to accommodate researchers who cannot share their data because of data-sharing restrictions. This study will provide the most comprehensive evidence on this topic to date and will deepen our understanding of suicidality among youth and adults with irritability across a wide range of cultures and populations, with the ultimate goal of informing clinical decision making.

Informant Effects on Reports of Irritability in Children and Adolescents. Informant effects refer to how questionnaire or interview responses differ according to whether the respondent is the youth, the youth's caregiver, a teacher, or another informant. Emerging evidence suggests significant differences between reports of irritability from different informants (eg, parents, caregivers, teachers, children/adolescents), and such reports vary based on age,[56] sex,[56] and the severity of irritability and diagnostic status.[57] For example, parents reported higher levels of irritability in male participants compared to female participants during childhood but not adolescence, whereas female adolescents self-reported more irritable mood compared to male adolescents.[56] Also, findings from the Texas Youth Depression and Suicide Research Network (TX-YDSRN),[58] a large-scale prospective study contributing to the C3I, demonstrated poor agreement between youth self-report and parent/guardian-report of irritability for both male and female participants.[59] Shared and unique irritability factors were identified from the combined youth and parent/guardian-report, indicating the importance of multiple informants. Furthermore, biological mechanisms underpinning irritability (such as association with polygenic risk scores) may vary based on the age of onset of irritability (childhood vs adolescence onset) or sex.[60] This project will leverage Consortium datasets to evaluate informant effects on reports of youth irritability. Specifically, we will study how informant effects vary across cultures and countries based on the child's age, sex, and biology (eg, serotonin transporter polymorphism). This project will help us to better characterize and understand informant effects on reports of irritability and their nuanced associations with the child's age, sex, and biological mechanisms across cultures.

Other Consortium Activities

Other C3I activities include the following: (1) Consortium-wide meetings and informal gatherings at standing conferences for members to connect, to exchange ideas, and to build collaborations; (2) website (http://m.yale.edu/c3i) and newsletters to feature C3I's work and to provide updates about C3I activities and initiatives; and (3) grant planning and applications to secure funding to build and sustain a productive international network (Supplement 1, available online, or C3I website).

TABLE 1 Key Information About the Three Ongoing Research Projects

Projects	Norms and empirical thresholds	Irritability and suicidality	Informant effects
Research questions	Do the norms and empirical clinical thresholds of irritability vary across cultures?	What is the association between irritability and suicide-related outcomes? Does the association vary across cultures?	Does the informant effect/agreement on irritability vary across cultures?
Datasets	Individual-level, deidentified, large cross-sectional epidemiological datasets of representative samples (Ns = 3,200-18,818)	52 Datasets (cross-sectional and longitudinal) from the C3I data repository measuring a suicide-related outcome (Ns = 50-12,000) (Figure S1, available online)	41 Datasets (cross-sectional and longitudinal) from the C3I data repository with self- and parent/guardian-reports of irritability. 12 Datasets with teacher-reports
Countries represented	Ethiopia, India, Japan, Peru, South Africa, Taiwan, UK, US, Vietnam	US (n = 32), Brazil (n = 2), Canada (n = 8), and other countries (n = 1 from Japan, Turkey, Taiwan, South Africa, Germany, and a pooled dataset from multiple countries)	US, Brazil, Canada, Japan, Turkey, and a pooled dataset from multiple countries
Total estimated N	~75,000	~40,000	~20,000
Age of the sample, y	0-22	0-65	0-18
Measures of irritability	ARI, CBCL, DAWBA, CAPA, SDQ, and reactive aggression items from SBQ	ARI, CBCL, KSADS, SDQ, and reactive aggression items from SBQ	ARI, CBCL, KSADS, SDQ, CAST-IRR and reactive aggression items from SBQ
Analytic approach	Data harmonization including natural language processing, latent variable modeling, eg, confirmatory factor analysis to test measurement invariance and item response theory to derive symptomatic thresholds. Norms will be generated for each country/culture and compared. Prevalence of severe, impairing irritability and age- and sex-related differences in irritability will be estimated and compared across countries and cultures.	An individual participant data (IPD) meta-analysis approach using deidentified data directly shared with the C3I as well as summary statistics generated locally using a harmonized analysis protocol.	An IPD meta-analysis approach using deidentified data directly shared with C3I as well as summary statistics generated locally by investigators using a harmonized analysis protocol.

(*continued*)

TABLE 1 Continued

Projects	Norms and empirical thresholds	Irritability and suicidality	Informant effects
Preliminary findings, if available	Preliminary results from a large representative sample of 6,137 children in Taiwan showed that the estimated prevalence of severe and impairing irritability was 2.6% and that relative to girls, boys had higher levels of irritability and greater decreases in irritability with age.	Preliminary finding suggests that childhood irritability is longitudinally associated with increasing risk of suicide attempt (including when adjusting for key covariates, eg, sex, socioeconomic status, concurrent internalizing symptoms) but not suicidal ideation. In adult clinical populations, irritability is cross-sectionally associated with suicidal ideation. Associations were similar for male and female participants.	There were significant differences between parent- and youth-report of irritability that may differ based on the child's sex (ie, in male participants, parent-report of irritability was higher than that in youth-report, whereas in female participants, the reverse was true). Moreover, parent–child agreement was lower in children who were homozygous or carriers of the short allele of the serotonin transporter, compared to those homozygous for the long allele.

Note: ARI = Affective Reactivity Index; C3I = Cross-Cultural Consortium on Irritability; CAPA = Child and Adolescent Psychiatric Assessment; CAST-IRR = Concise Associated Symptom Tracking—Irritability; CBCL = Child Behavior Checklist; DAWBA = Development and Well-Being Assessment; KSADS = Kiddie-Schedule for Affective Disorders; SBQ = Social Behavior Questionnaire; SDQ = Strengths and Difficulties Questionnaire.

DISCUSSION

An Invitation to Colleagues Around the Globe

Since C3I was launched in May 2022, it has attracted many researchers and clinicians around the globe who are interested in the cultural aspects of irritability. Nonetheless, about 40% of the members are from the United States. This publication is designed as an open call for more researchers, scholars, and clinicians around the globe to join C3I. Anyone who wishes to participate in any C3I activities is welcome to contact the C3I Chair (Dr. Wan-Ling Tseng; see corresponding author information) or the respective Working Group Chair or project lead. As part of our effort to increase participation from as many countries and regions as possible, we extend a special invitation to individuals in regions and countries who are currently unrepresented in the Consortium. Participation in, and contribution to, this Consortium from individuals with varied perspectives are key to advancing the field's understanding of the cross-cultural differences and similarities in irritability.

Summary

Irritability is a highly prevalent problem in youth seeking mental health services[2] and is a robust predictor of later mental health problems, including suicide-related outcomes.[6–8] However, most of the extant literature on irritability is conducted by researchers from HICs working in majority samples from their own countries. Thus, the extent to which past findings generalize across various cultures, LMIC countries, and underrepresented populations remains to be determined. C3I aims to fill this gap through cross-cultural data-pooling and research, generating empirical insights on cultural variation in the following: (1) the norms and clinical thresholds of irritability; (2) the link between irritability and suicidality; and (3) informant effects. These efforts are expected to accelerate C3I's growth in the coming years by increasing the Consortium's visibility. In turn, attracting more researchers/clinicians interested in irritability around the globe will facilitate further cross-cultural collaboration. We hope readers will join us in our ongoing efforts to advance cross-cultural research on irritability in order to build a robust evidence base needed to benefit the largest possible number of children and adolescents experiencing irritability worldwide.

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