Need for Standardization of Yoga Protocols In Research

EXPERT MEETING
BENEFITS AND BARRIERS OF YOGA
RESEARCH
PGI Chandigarh
Jan 9th 2024
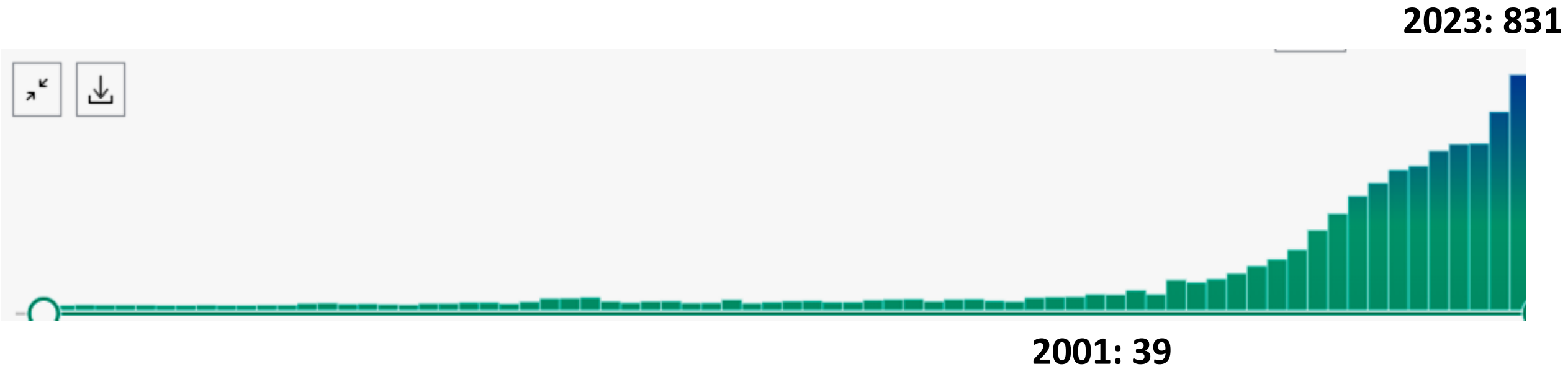
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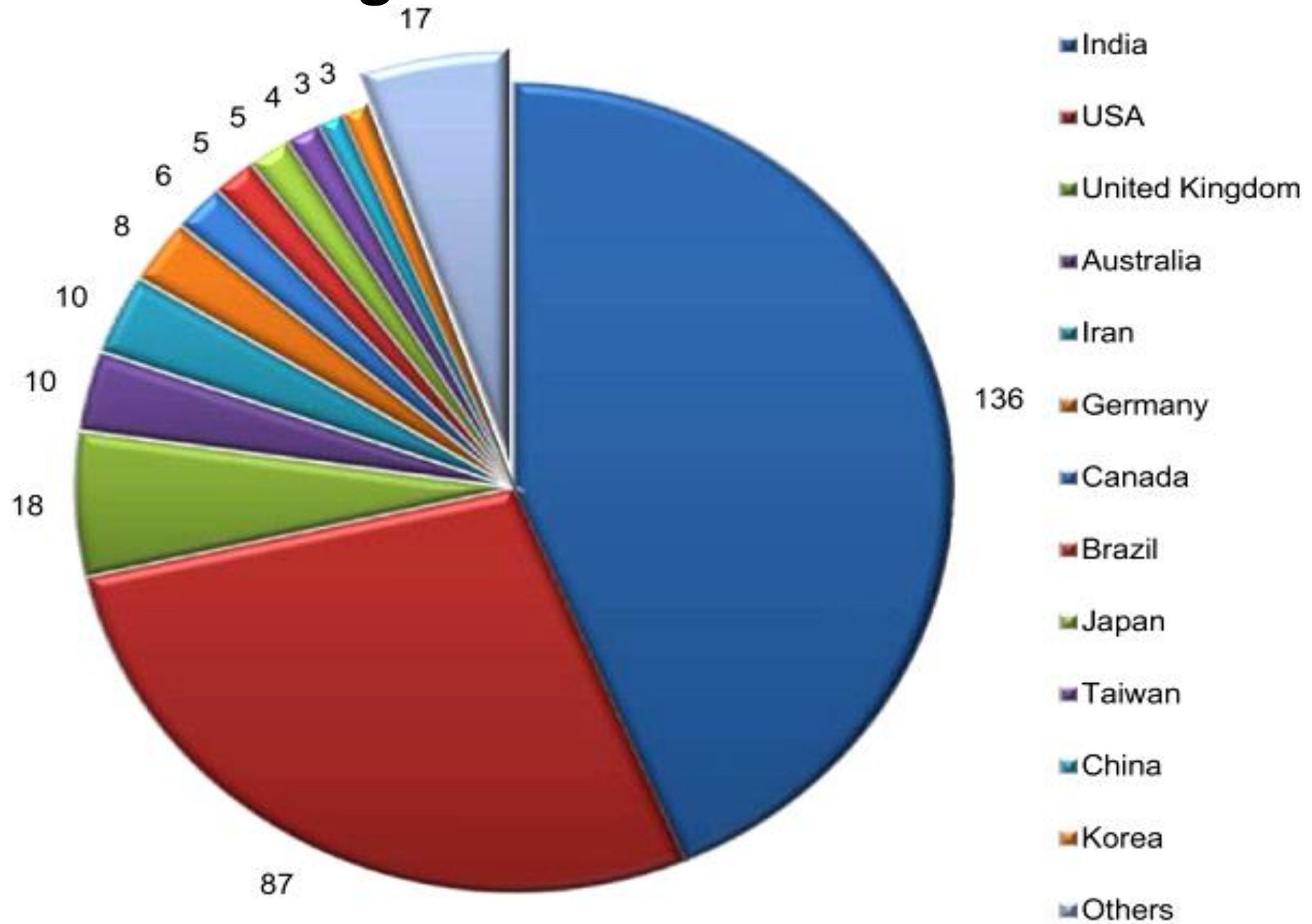**National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, South India**

Greetings from the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, South India

Yoga Research Trend: Hits on PubMed with Keyword "Yoga"

2023: 831

2001: 39

RCTs on Yoga from Different Countries

Legend:
- India
- USA
- United Kingdom
- Australia
- Iran
- Germany
- Canada
- Brazil
- Japan
- Taiwan
- China
- Korea
- Others

Values: 136, 87, 18, 10, 10, 8, 6, 5, 5, 4, 3, 3, 17

4

Type of yoga	Key features
Ashtanga yoga	Fast-paced series of sequential posture, based on six series of asanas
Hatha yoga	Basic form of yoga which incorporates postures, regulated breathing, and meditation
Iyengar yoga	Focuses on the precise alignment of postures
Power yoga	Westernization of Ashtanga yoga. Popular in the US
Jivamukti yoga	Physically challenging postures, highly meditative
Kali Ray TriYoga	Consists of flowing, dance-like movements, often accompanied by music
White Lotus Yoga	Consists of flowing movements with varying difficulty levels
Integrated yoga therapy	Designed for medical problems. May include meditation and guided imagery
Viniyoga	Gentle practice which particularly emphasizes on the synchronization of poses with breathing
Sudarshan Kriya Yoga	Series of forceful inhalations and exhalations at different rates with chanting 'so-ham'

Type of yoga	Key features
Svaroopa	Emphasizes on the "opening of the spine beginning at the tailbone progressing through each spinal area"
Bikram Yoga (Hot Yoga)	Consists of a series of 26 postures performed in a space with temperature above 100°F
Phoenix rising yoga therapy	Combines traditional yoga with client centered and mind-body psychology, that incorporates non-directive dialog
Sivananda yoga	Consists of 12 basic yoga postures along with chanting and meditation
Integral yoga	Consists of basic hatha yoga postures
Ananda yoga	Consists of basic hatha yoga postures with use of "silent affirmations while holding up a pose"
Kundalini yoga	Focuses on awakening the energy at the base of the spine and channeling it upwards
ISHTA yoga	Combination of Ashtanga and Iyengar yoga
Kripalu yoga	Consists of three stages namely willful practice, willful surrender, and meditation in motion

- **Different trials use different techniques of yoga**

- **This is a major hindrance in clinical applications of Yoga**

- **Hinders scalability of interventions**

- **Hinders cross-cultural applications**

Generic Yoga Modules for Clinical and Research Settings–Need of the Hour

Vinod Kumar [1], Aarti Jagannathan [2], Hemant Bhargav [3], Shivarama Varambally [4], B N Gangadhar [5]

Affiliations + expand

PMID: 34260713   DOI: 10.17761/2021-D-18-00016

Abstract

Yoga-based interventions offer significant promise in healthcare. However, meta-analyses of various yoga trials suggest that comparisons of trials are either not possible or difficult due to heterogeneity in therapeutic yoga interventions. Also, in view of emerging evidence for the role of therapeutic yoga, it is important to identify the specificity and validity of various yoga components being used in different trials. Efforts in this direction will be fruitful only if a systematic approach is adopted to develop yoga programs for various ailments. In this article, we emphasize the need for a "generic yoga" concept for designing a therapeutic yoga program for particular health issues, with the objectives of promoting scientific growth of therapeutic applications of yoga and widespread application of standardized therapeutic yoga programs within a biomedical framework. This generic therapeutic yoga will essentially highlight the development-validation process of uncopyrighted yoga programs; their components, benefits, and possible side-effects; and requirement for need-based modifications.

Keywords: generic; standardization; therapeutic yoga.

PubMed Disclaimer

"Generic" Yoga Modules

- **Schizophrenia**
- **Depression**
- **Mild Cognitive Impairment (MCI) & Dementia**
- **Attention Deficit Hyperactivity Disorder (ADHD)**
- **Somatoform Disorders**
- **Obsessive compulsive Disorder (OCD)**
- **Substance Use Disorder**
- **Parkinson's disease**
- **Generalized Anxiety Disorder**
- **Caregiver**
- **Teleyoga for stress**
- Migraine
- Epilepsy
- Autism

Modules developed at NIMHANS

In progress

Yoga Module Development and Validation: A Systematic Review with Methodological Guidelines

Naresh Katla [1], Atmika Ramsahaye [2], Arun Thulasi [2], Judu Ilavarasu [1], Aarti Jagannathan [3], Hemant Bhargav [4], Shivarama Varambally [5], Nanjudaiah Gangadhar [6]

Affiliations + expand
PMID: 36949837   PMCID: PMC10026335   DOI: 10.4103/ijoy.ijoy_59_22

Free PMC article

Abstract

In the past decades, more than fifty different yoga styles have been implemented in the therapeutic context to manage various diseases. Yet, not all of these yoga styles have been validated or standardized as a program. The aim of this article is to review the different methodologies used for yoga module development and to assess their quality. Three databases (PubMed, Web of Science, and Scopus) were searched using the following keywords and Boolean operators: (validation OR development OR design) AND (yoga OR mind-body) AND (module OR protocol OR program). Three thousand six hundred and seventy-one articles were enlisted, and based on the inclusion and exclusion criteria, 37 articles were narrowed down for review. Since no checklist exists to assess the quality of yoga modules, the authors designed a 23-item checklist to categorize each having low, medium, or high quality. As per the yoga module quality checklist, only 21.6% of the studies had high quality, while 75.3% of the articles had medium quality and 8.11% had low quality. A commonly used development method was literature review, while for validation, experts' scoring of the Likert scale was the preferred means. The feasibility of the module was carried out only by half of the studies. Few diseases such as cardiovascular disease, diabetes mellitus, obesity, Parkinson's disease, and obesity had more than one yoga module developed. The findings of this systematic review have shed some light on the growing need for standardized methods of yoga module development. The 23-item checklist can guide researchers in the homogeneous development

23-item Checklist to Assess Generic Yoga Module Development Process

Yoga module development

1	Traditional literature review
2	Scientific literature review
3	Dose, frequency, and duration of intervention
4	Involvement of experts, clinicians, and participants in the development phase
5	Yoga practice sequence
6	Customization of practices
7	Instructor qualification
8	Reporting adverse effect
9	Home practice details

Yoga module validation

10	Professional eligibility of experts
11	Diversity of experts
12	Details of the items provided to experts
13	Involvement of stakeholders
14	Expert content validation
15	Group discussion
16	Use of case vignettes
17	Involvement of stakeholders

Intervention

Yoga Group

Buprenorphine/Naloxone
+
Psychosocial support

+

Validated Yoga Protocol
Duration: 24 weeks
2 weeks Direct + 22 weeks Tele-mode

Trained Yoga therapist
(M.Sc. Yoga Therapy)

2

Acute Withdrawal Phase
Duration: 40 minutes

Maintenance Phase
Duration: 60 minutes

Physical Postures
40%

Breathing techniques
20%

Guided Meditation
15%

Guided Relaxation
25%

Butterfly pose

Straight Leg Raising

Crocodile pose

Cobra pose

Wind Relieving Pose

Alternate Nostril
Breathing

Bellow's Breath

Humming Breath

Nadanusandhana

Deep Relaxation Technique

Waitlist Control Group

Standard Treatment
Duration: 24 weeks

Buprenorphine/Naloxone
+
Psychosocial support

([1]Bhargav et al. 2022)

Preliminary Work – Yoga and SUD

- **Yoga Module Development*:** Development, content validation and feasibility testing – 8 patients – 10 sessions (5days/week) – safe, easy to learn, reduction in pain, anxiety, sleep latency, CGI-severity.[1]

- **Tele-yoga for Substance Use Disorders:** In patients with SUD (n = 30; n = 8, AUD): 1-month tele-yoga – 5 days/week – 70% completed the study; safe and feasible.[2] Good inter-therapist reliability.

- **RCT on patients with AUD (N = 60):** Two week yoga intervention improved plasma cortisol, ACTH and BDI (depression scores).[4]

- **Increase in plasma beta-endorphin levels:** Immediately after practicing validated yoga module in healthy subjects as well as in OUD patients

- **Alcohol Cue-Craving fMRI paradigm:** Visual Image-Induced Craving for Ethanol (VICE): : Development, Validation, and a Pilot fMRI Study[3]
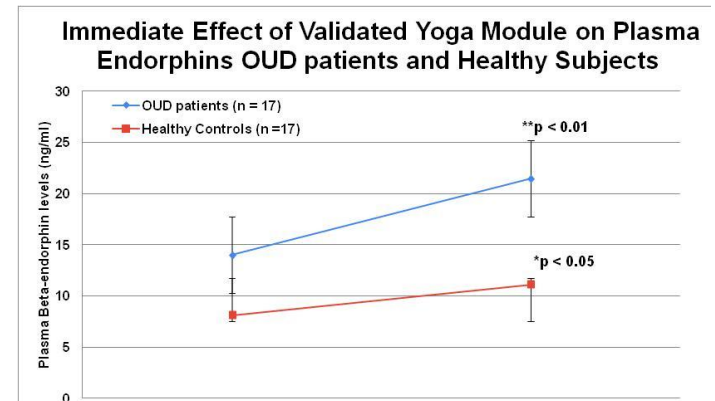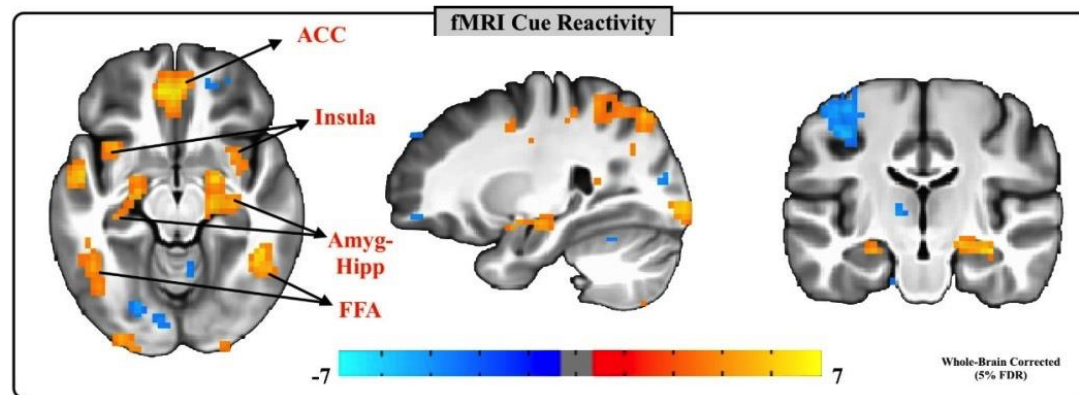
(1Bhargav et al, 2020
2Bhargav et al, 2021
3 Holla et al, 2014
4Vedamurthachar et al, 2005)

fMRI Cue Reactivity — ACC, Insula, Amyg-Hipp, FFA. Whole-Brain Corrected (5% FDR)

Immediate Effect of Validated Yoga Module on Plasma Endorphins OUD patients and Healthy Subjects. OUD patients (n = 17), Healthy Controls (n =17). Plasma Beta-endorphin levels (ng/ml). $**p < 0.01$, $*p < 0.05$

Alcohol Use Management using Yoga as an Adjuct Modality (AUMYAM): A Multi-centric Randomized controlled trial

Why Yoga for Substance Use Disorders (SUDs)?

- Yoga reduces
    - depression, anxiety and stress in patients with SUDs *(Saeed et al, 2019)*
    - chronic pain and enhances plasma endorphin levels in patients with common NCDs *(Büssing et al, 2012; Yadav et al, 2012)*
    - clinical symptoms in SUDs , is safe and feasible in patients

        (Sarkar, 2017; Bhargav et al, 2021; 2022)

- Tele-yoga is a feasible and useful in SUD patients with good inter-rater reliability (r = 0.77) *(Bhargav et al, 2022)*

- Yoga is free from social stigma, culturally acceptable and accessible, and promotes pro-social behavior

    (Mishra 2017)

Yoga Research in Substance Use Disorders (SUDs)

- Evidence suggests utility of Yoga in
  - stress[5], depression[6], anxiety[7], schizophrenia[8] and chronic pain[9]
  - Long-term Practice → **neuroadaptive** changes
- Yoga is culturally acceptable[11], accessible,

Yoga in addiction: 17 RCTs[6,7] (4 RCTs in AUD*)

Most commonly studied	Less commonly studied	Need to study (Current plan)
Quality of Life[15,16,17,18]	Biological Variables (Cortisol)[19]	Core Addiction Outcomes (Abstinence, Craving, Pain)
Mood[16,18,19,20,21]	Abstinence[23-25]	Brain Mechanism (fMRI Cue-Reactivity)
Stress and Anxiety[19,20,21]	Craving[26,27] Psychophysiology[26]	Biomarkers of Response (Endorphin, Cortisol, & HRV)

*AUD: Alcohol Use Disorder
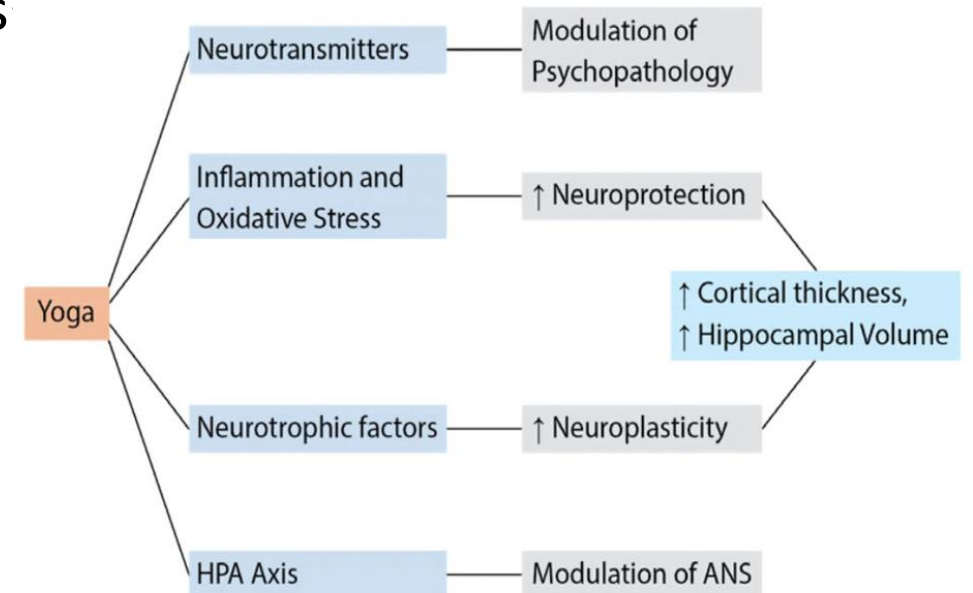
Yoga and psychiatric disorders: a review of biomarker evidence

(Bhargav et al, 2021)

([5]Saeed et al, 2019; [6]Cramer et al, 2013; [7]Cramer et al, 2018; [8]Rao NP et al, 2021; [9]Büssing et al, 2012; [10]Hernández et al, 2020; [11]Mishra et al, 2017; [12]Bhargav et al, 2021; [13]Sarkar, 2017; [14]Kuppili et al, 2019 [15]khalsa 2008; [16]Zhuang et al, 2013; [17]Dhawan et al, 2015; [18]Devi et al, 2014; [19]Vedamurthachar, 2006, [20]Sareen et al, 2007, [21]Marefat et al, 2011; [22]Sharma 2006; [23]Kochupillai, 2005; [24]Bock et al, 2012; [25]Mallik et al, 2019; [26]Eliberto et al, 2011, [27]Shahab et al, 2013)

Yoga for Substance Use Disorders: Current Evidence

• Three Narrative Reviews involving 17 RCTs (7 RCTs in Tobacco Use Disorder, 4 RCTs in AUD, 3 in OUD, 1 Multiple, 2 Unspecified)
- beneficial effects as an adjunctive treatment in substance use disorders

(Kupilli et al, 2018; Sarkar, 2017; Khanna 2013)

• Recent systematic review of 8 RCTs (2 – AUD, 2- TUD, 2- OUD and 2- Undefined Substance)
- Seven out of 8 studies showed significant results and improved outcomes of using yoga in conjunction with other pharmacological treatment modalities
- The primary outcomes showing improvement were **anxiety, pain, and substance use.**

(Walia et al, 2021)

•Core addiction clinical symptoms have not been focussed much in previous researches. Only two 6 month follow-up studies so far.

Objectives and Study Design

Primary:	To evaluate the effect of **6-month add-on Yoga-based intervention** on clinical outcomes **(alcohol abstinence, and craving)** in patients with AUD as compared to standard treatment alone.
Secondary:	*Biological* (transcriptomics, cue-craving fMRI, beta-endorphin, BDNF, cortisol and HRV); *Clinical* (sleep quality, depression, anxiety, withdrawal symptoms); *Psycho-social* (work and social adjustment) and *Psychological* (yoga-based mental attitudes –gunas, perceived stress), *Yoga performance assessment* (YPA)

Clinical Assessments:	Alcohol Use Disorder (as per DSM5 criteria) –MINI plus and clinical interview to rule out psychiatric comorbidities (qualified psychiatrist). Further Details on Optimization in Supplementary material.

Randomized (n=164) Assessor Blind Parallel-Arm	Intervention	Standard Treatment (BPN-OST + Psychosocial Support)				(n=82)			
		Standard Treatment (BPN-OST + Psychosocial Support) +				(n=82)			
		Supervised Yoga	Tele-Yoga						
		(2w - 10 sessions)	(22w)						
Assessments		**BL**	**2w**	**1m**	**2m**	**3m**	**4m**	**5m**	**6m**
Clinical Outcomes (Abstinence*, Craving)		x	x	x	x	x	x	x	x
Cue-Craving fMRI		x				x			x
Beta-endorphin		x				x			x
Serum Cortisol & BDNF		x				x			x
Anxiety, depression & Withdrawal symptoms		x	x x x x x x x x x x				x			x
Others**		x	x				x			x

Sample size Estimation for Multivariate Linear Mixed Models

ES~0.4 (medium) [1-3]
α=0.05
Power=0.90
Req N = 60 in each group
36% drop out at 6 months [4]
82 in each group.
Interim analysis to reassess exact sample size required

([1]Mallik, et.al. 2019, [2]Eliberto et al, 2011, [3]Yadav et al 2012, [4]Dhawan, et.al. 2015 and our pilot study)

Research Question:

Is Adjuvant Yoga therapy effective in promoting abstinence from Alcohol consumption in Alcohol dependents?

Primary Objective:

To assess the effect of Yoga therapy on abstinence from Alcohol consumption in patients with Alcohol dependence

Secondary Objectives:

1. To assess the effect of Yoga therapy on transcriptomics in patients with Alcohol dependence (in relation with craving reduction)
2. To assess the effect of Yoga therapy on biomarkers in patients with Alcohol dependence
3. To assess the effect of Yoga therapy on Anxiety and Depression in patients with Alcohol dependence

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┌─────────────────────────────────────────────────────────────────────────┐
│   Screening of Two weeks of detoxification/medically stable patients'     │
│                     Alcohol Dependence as per ICD-10                       │
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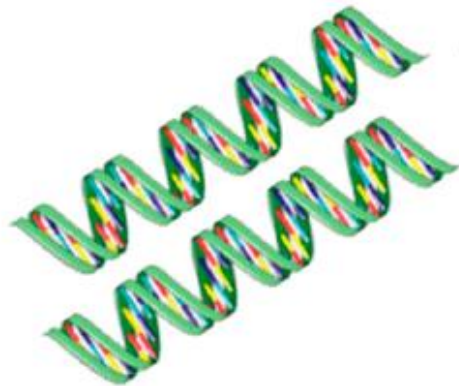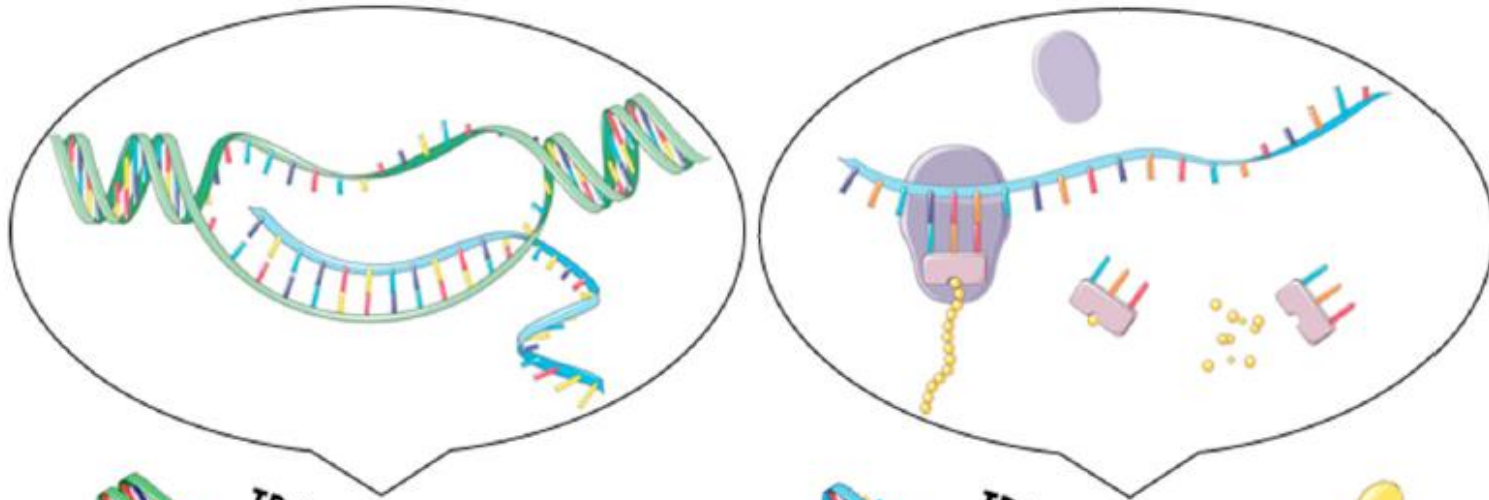| Participants randomly assigned to medication/counselling (n=82; per centre)	Participants will be randomly assigned to medication/counselling +Yoga Intervention (n=82; per centre)
Psychiatric assessment: HAM-D, HAM-A, ACQ-SF-R, CIWA-Ar, ISI **Blood: Cortisol, GT, CDT** **Sub group analysis of Transcriptomics (n=40)**	**Psychiatric assessment: HAM-D, HAM-A, ACQ-SF-R, CIWA-Ar, ISI** **Blood: Transcriptomics, Cortisol, GT, CDT** **Sub group analysis of Transcriptomics (n=40)**
Counselling every week for 24 Weeks	**24 Weeks Yoga Intervention**
Psychiatric assessment: HAM-D, HAM-A, ACQ-SF-R, CIWA-Ar, ISI **Blood: Cortisol, GT, CDT** **Sub group analysis of Transcriptomics (n=40)**	**Psychiatric assessment: HAM-D, HAM-A, ACQ-SF-R, CIWA-Ar, ISI** **Blood: Cortisol, GT, CDT** **Sub group analysis of Transcriptomics (n=40)**
Monthly Follow-up for next 24 weeks to monitor relapse	**Monthly Follow-up for next 24 weeks to monitor relapse**

Outcome measures

Primary: Abstinence assessment: Self reported No. of days of abstinence and validated through EMA and EMI.
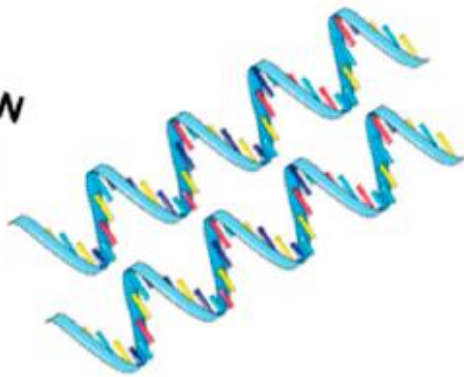
Secondary:

1. **Psychiatric assessment**: Hamilton Depression & Anxiety Scales (HAM-D/A), and Alcohol Craving Questionnaire-Short Form-Revised (ACQ-SF-R), Clinical Alcohol withdrawal scale, carving assessed by validated fMRI cue craving paradigm.

2. **Blood serum**: Cortisol, BDNF, Plasma Endorphins, Gamma Glutamyl Transferase (GT), Carbohydrate-Deficient Transferrin (CDT)

3. **Transcriptomics:** (protein trafficking, myelin, and oligodendroglial cells)

(Pathway analysis revealed differential expression in genes involved in protein trafficking, myelin, and oligodendroglial cells in alcohol-dependent patients.)

Thank You

GENOMICS (DNA)

genetic tests
gene panel sequencing
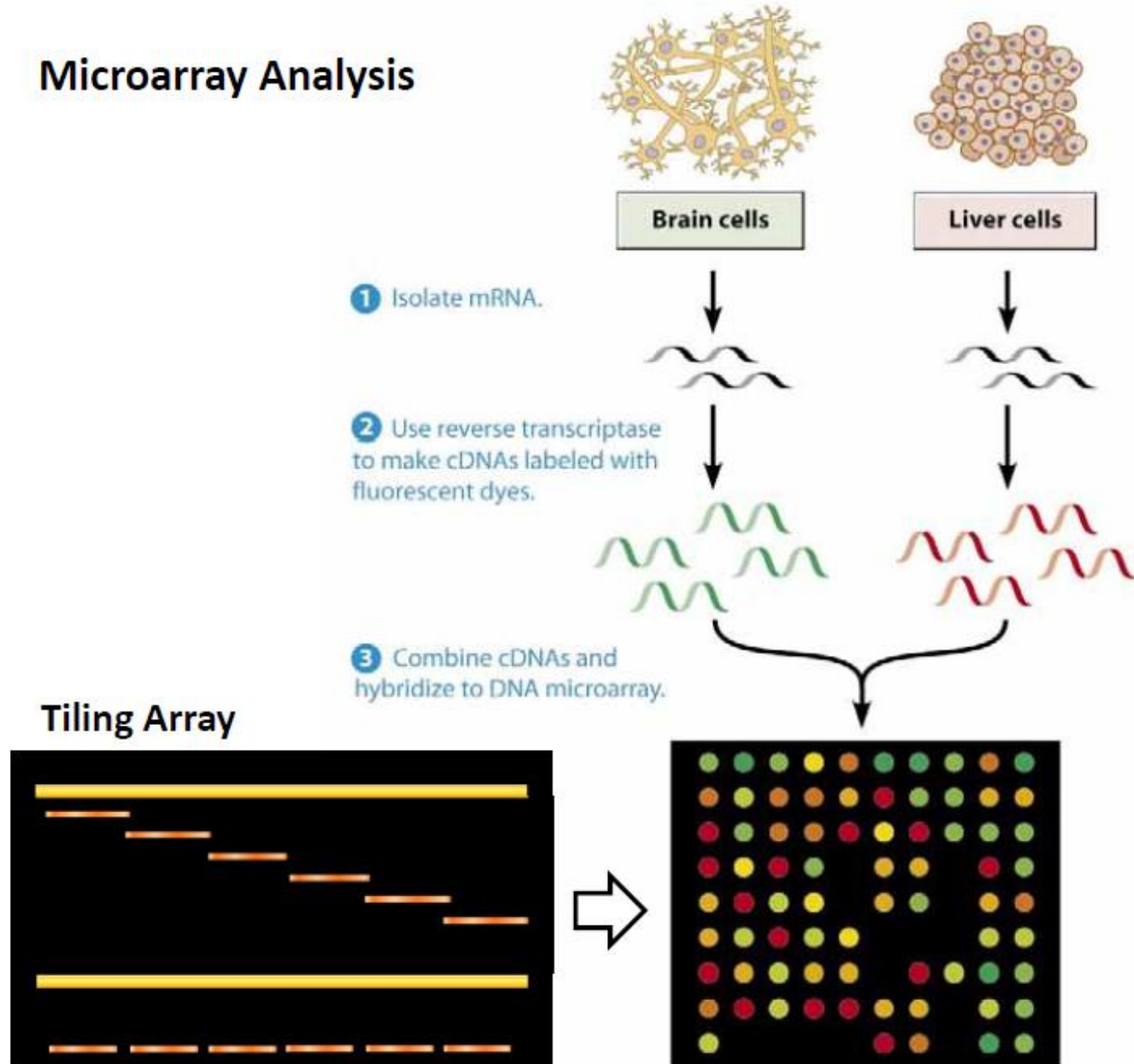whole exome sequencing

TRANSCRIPTOMICS (RNA)

RNA sequencing
RNA microarrays

PROTEOMICS (PROTEINS)

protein arrays

TRANSCRIPTION

TRANSLATION

Experimental Approaches Used to Characterize the Human Transcriptome

Microarray Analysis

Brain cells   **Liver cells**

1 Isolate mRNA.

2 Use reverse transcriptase to make cDNAs labeled with fluorescent dyes.

3 Combine cDNAs and hybridize to DNA microarray.

Tiling Array

① Isolate mRNAs from cells at two stages of development; each mRNA sample represents all the genes expressed in the cells at that stage.

mRNA

② Convert mRNAs to cDNAs by reverse transcriptase, using fluorescently labeled deoxyribonucleotide triphosphates.

reverse transcriptase

cDNA

③ Add the cDNAs to a microarray; fluorescent cDNAs anneal to complementary sequences on the microarray.

DNA microarray

Removal of unhybridized probe

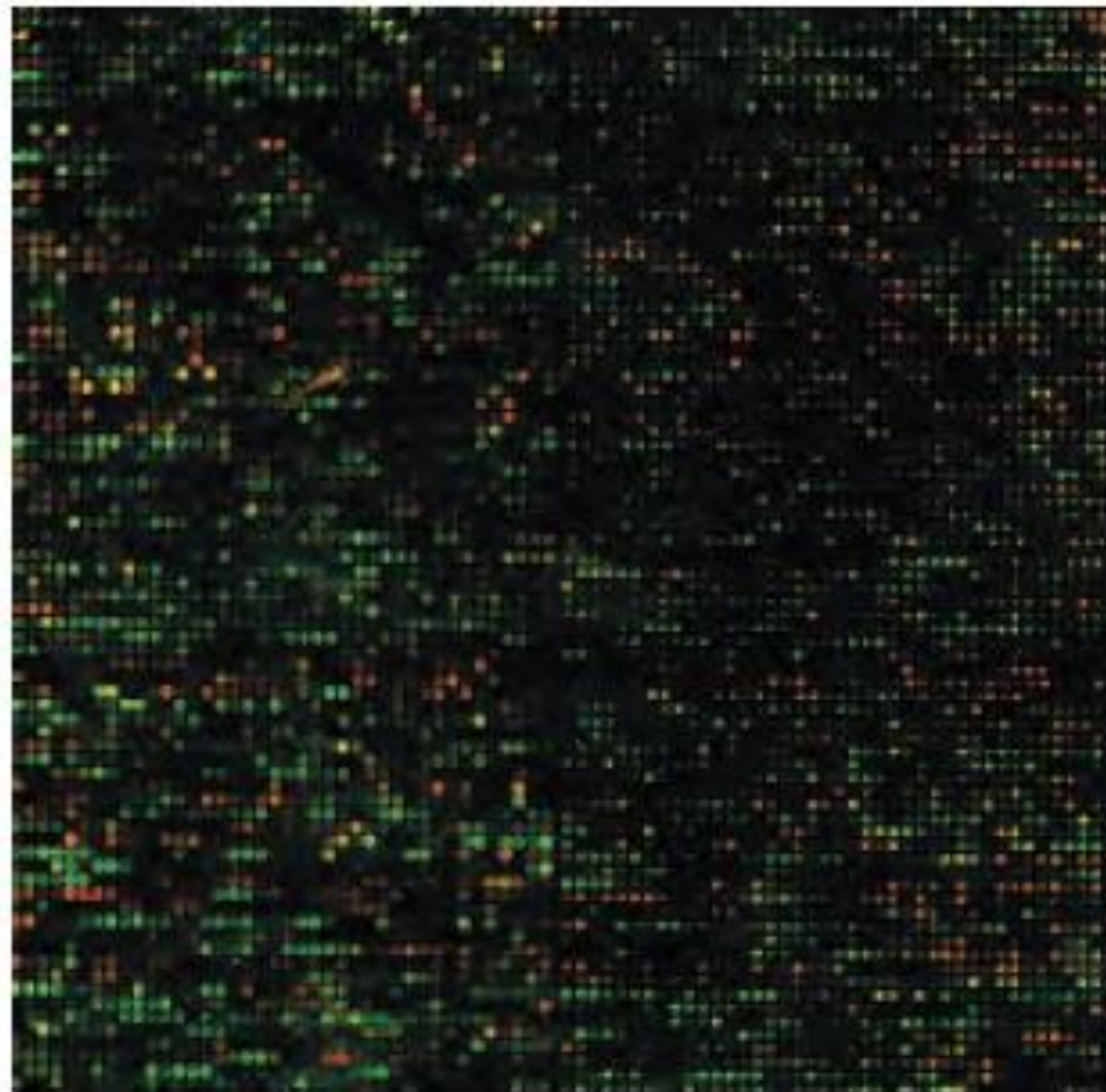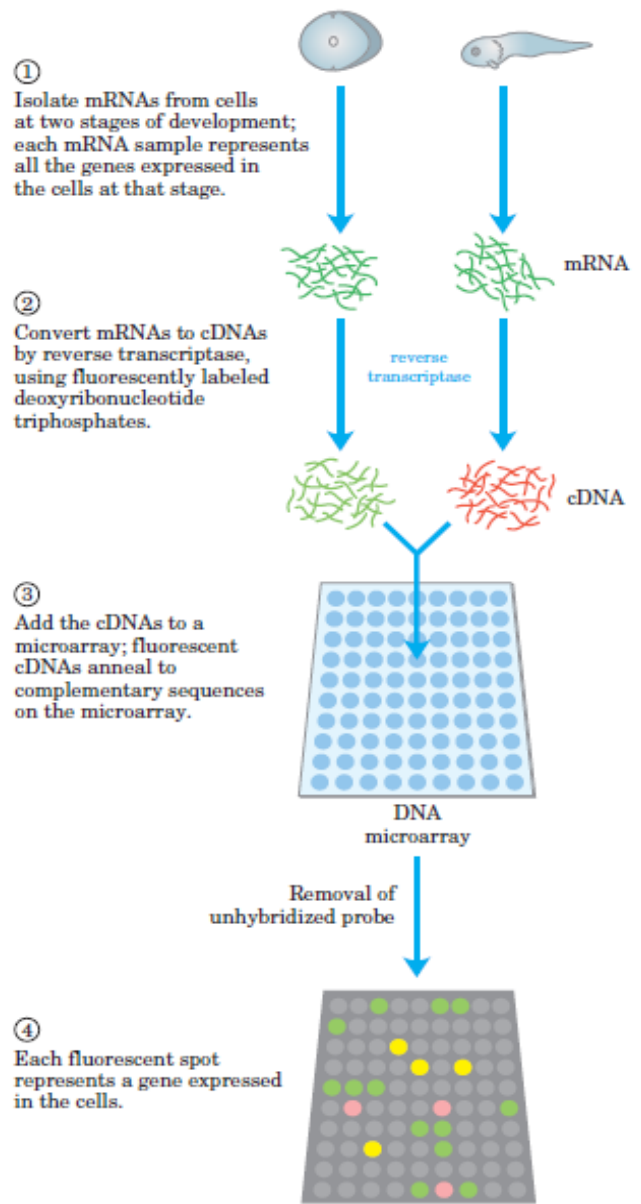④ Each fluorescent spot represents a gene expressed in the cells.

Table Box 1 Algorithm to Prioritize Genes that Change in Disease and Response to Treatment

I. Statistical considerations based on gene changes in multiple studies

A gene fold change from control and the significance (p-value) and reproducibility of that change are assigned a 'statistical score':

Fold change score = the fold change if gene increases, and $1/\%$ of control value if the gene decreases

p-Value score = $-\log_{10}(p\text{-value})$

Reproducibility score = $\times 2$ for 1 replication of co-directional, statistically significant gene change, $\times 4$ for 2 replications

Statistical score = (fold change score $\times$ p-value score)reproducibility score

II. Biological considerations based on human and animal studies of the gene that changed

A. Gene change is in the same direction of mRNA or protein change in human disease

B. Gene change is in the same direction of mRNA or protein change in animal model of the disease

C. Gene or its protein product change in the opposite direction in animals by treatments for that disorder, or when manipulated in transgenic animal, it models part of the disease pathology

D. Gene is part of a biochemical pathway associated with human disease or its treatment

E. Gene's human homolog is in a chromosomal hot spot for disease as identified by linkage analysis

Biological score = A (10)+B (8)+C (8)+D (5)+E (2); maximum = 33

The values in parentheses are summed for each criterion that is true for A–E

III. Pharmacological considerations

The score is based on how 'drugable' the target is, and whether it has received support in the past as a drug target

A. Gene changes in disease or in response to therapeutic agents are found to be under the control of a drugable target (ie, receptor or enzyme antagonist)

B. For antagonist approach, knockout of the target mimics the desired gene changes, or overexpression mimics the disease phenotype. Gene changes are reversed in knockout model by effective drugs.

C. Gene or its protein product is changed by effective treatments for that disorder or when manipulated in transgenic animal, predictably affect disease pathology.

Pharmacological score = A (10)+B (9)+C (8); maximum = 27

The values in parentheses are summed for each criterion that is true for A–C

Algorithm score = Statistical score+biological score+pharmacological score

Example of a robust gene:

A gene is doubled in bipolar disorder with a p-value of 10^{-5}, and its increase is replicated in two other studies. If the gene fulfills all biological and pharmacological criteria, its algorithm score will be about the maximum, or $(2 \times 5) \times 4+33+27 = 100$

This algorithm includes features that have been used to identify genes associated with schizophrenia (Altar *et al*, 2008) and the therapeutic response to ECT (Altar *et al*, 2005). The statistical, experimental, biological, and pharmacological considerations are quantified and summed to prioritize the significance of each gene as a target for CNS drug discovery.