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Research Article

Bibliometric Analysis of Published Literature Utilizing Optogenetics as a Technique in Neuroscience: 2010–2020

Dwight Figueiredo[1,*], Paulomi Sanghavi[2]

[1]Symbiosis Institute of Health Sciences (SIHS), A Constituent of Symbiosis International (Deemed to be University) (SIU), Pune, Maharashtra, INDIA.
[2]Department of Biological Sciences (DBS), Tata Institute of Fundamental Research, Mumbai, Maharashtra, INDIA.

ABSTRACT

The optogenetics technique where in light is used to excite or inhibit neurons has uncovered many new brain neuronal circuits causal in or associated with routine day-to-day physiological functioning as well as complex emotions/behaviors. The optogenetics technique due to its virtue of high spatial and temporal specificity, has uncovered neural correlates of organism functioning and behavior at a cellular/sub-cellular resolution, something not possible before in Neuroscience. Using the SciVerse Scopus database, we analyzed neuroscience based published literature (i.e., articles and reviews) utilizing Optogenetics as an investigative tool between years 2010 to 2020. 6568 published documents were refined to 2621 documents after using the appropriate filters in Scopus. The average retrieved document count per year was 262, with an over all *h*-index at 128. Karl Deisseroth and Edward S. Boyden were the two leading authors in the neuroscience optogenetics domain. The highly used author keywords in optogenetics were pertaining to *in vivo* models used, cell types and brain regions studied, etc. Top-cited documents in optogenetics were focused on optogenetics as a versatile developing tool, and its applicability as an investigative tool in diverse neuroscience domains. Thus, the increasing volume of published literature utilizing optogenetics signifies its enormous contribution as a discovery-based tool.

Keywords: Optogenetics, Neuron excitation, Neuron inhibition, Circuits, Behavior, VOSviewer.

Correspondence:
Dwight Figueiredo
Symbiosis Institute of Health Sciences (SIHS), A Constituent of Symbiosis International (Deemed University) (SIU), Pune-412115, Maharashtra, INDIA.
Email id: dwight.fig@gmail.com
ORCID ID: 0000-0003-4548-1998

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INTRODUCTION

Our initial understanding of the involvement of the Central Nervous System (CNS) regions and circuits in functional behavioral output mainly rested on crude techniques such as electrode stimulation of brain areas, brain lesion studies, and pharmacological interventions.[1-4] However, the non-specificity of these interventions made deciphering specific neurons and circuits involved in the particular investigated behavior among heterogeneous populations difficult to pinpoint. Thus, assigning the activity of specific neuronal populations with heterogeneous brain regions to be the underlying cause of distinct normal and abnormal physiology or behaviors became complicated and frustrating.

Electrophysiological recording in brain slices and *in vivo*, along with pharmacological approaches, did allow for a dissection of neural circuitry related to functional outcomes.[5-7] Further more, technology to implant multichannel electrodes in brain regions evolved and activity at the level of single neurons could be obtained.[8-11] However, gaining stable high-quality recordings of single unit activity in certain hard-to-interrogate brain regions in awake moving animals while they carried out behavioral tasks proved to be technically difficult.[12,13] Moreover, the single units recorded are sometimes difficult to decode given the heterogeneity of distinct neuronal populations in those recorded regions.[14,15]

Genetically encoded calcium indicators with high regional and cellular specificity did help with neuronal activity monitoring at the population as well as to some extent at single cell resolution.[16-18] However, these technologies are not able to manipulate the activity of genetically defined cell types within heterogeneous brain regions with a level of spatial and temporal precision that could identify cause-effect relationships.

With the rapid development and coming together of three independent and mutually exclusive areas, 1. Applicability of light sensitive bacterial Rhodopsins to eukaryotic systems. 2. Non-genetic and genetic based *in vitro* and *in vivo* targeting strategies, and 3. The optical neural interface technology required for light delivery and recording *in vivo* optogenetics has become a mainstay technique in neuroscience to unravel the causal and associated neural underpinnings of physiological functioning, behavior, and CNS diseases (Table 1 for key publications, first

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author names, journals, year of publication, and times cited in these three complementary areas). The advantage of optogenetics compared to other techniques is its superiority in terms of cellular specificity and stimulation/inhibition temporal control (i.e., genetically defined cell population at millisecond level precision).

By year 2010, optogenetics was well established as an important technique in neuroscience which could be used to answer a multitude of hypothesis and question.[19-21] Originating from the lab of Karl Deisseroth at Standford (in 2005), optogenetics spread to neuroscience labs in the United States and all across the globe between 2005 to 2010.[22-24] Many neuroscience investigators have used optogenetics as a technique to answer challenging questions in their areas of specialization that were not adequately addressable before the advent of optogenetics.[25-27] Keeping this in mind, we wanted to conduct a bibliometric analysis of neuroscience literature utilizing optogenetics as a technique. Utilizing bibliometrics, we wish to address the following objectives: i) Identify the most productive and impactful authors in optogenetics, ii) Identify author collaborative networks, iii) Conduct a citation analysis of literature and highlight important contributing publications by means of number of citations, and iv) Ascertain the most productive and collaborative journals, institutions, and countries. Towards this end, we conducted a bibliometric analysis on optogenetic based literature (i.e. articles and reviews) in neuroscience using the Scopus SciVerse database. With the ever-increasing use of optogenetics in neuroscience and other non-neuroscience fields, along with yet-to-be discovered applications, optogenetics as a technique still has enormous potential with a long way to go.

METHODOLOGY

Bibliographic database

In this study, Scopus was the database that was used due to its vast scientific, technical, medical and social sciences coverage.[28] It being the largest database and its easy-to-use analytic functions made it a database of choice.[29] The choices of filters used are given in supplementary Figure 1. In our analysis, we chose to include only journal articles and journal reviews, as these types of documents contains majority of the scientific findings and literature in the optogenetics area. This is the case since optogenetics is a technique applicable to many a neuroscience research question.

Search strategy and validity

In order to obtain documents using optogenetics in a neuroscience-based context, we used the following search string in Scopus: "((optogenetics) AND ("Neuroscience" OR "Nervous system"OR "Brain" OR "Circuit*" OR "inhibit* neuron*" OR "excite* neuron*"))". Using this Search String in SCOPUS, we obtained 2621 documents. For validity of the above search strategy, authors manually checked 100 articles which were the top 10 cited articles for each of the top 10 authors during the study period.

Besides having no false positive results in our manual analysis, all of the documents scanned contained optogenetics in a neuroscience related context indicating correct scope.

Data Analysis

Bibliometric indicators/parameters such as highest number of citations, country productivity, authorship, citation analysis, annual growth, document type were presented as frequency and percentage. Annual Growth Rate (AGR), Relative Growth Rate (RGR), DT, citation count and characteristics, and quality of publications Hirsch index (*h*-index) were calculated and/or presented as in previous studies.[30-33]

Collaboration and authorship analysis

Number of single authored articles and number of multi-authored joint articles were calculated in excel. Overall collaborations in the form of Degree of collaboration, Collaborative Index (CI), Average number of Authors Per Paper (AAPP) were calculated and presented as before.[32,33]

Visualization and mapping

VOSviewer program was used to visualize bibliometric networks of author collaborations, country collaborations, institutional collaborations, Journal co-citation collaborative analysis,[34,35] Network visualization was chosen as the mode of presentation, with color (one cluster or group of close units), circle size (greater productivity or citations), font size, and thickness of connecting lines strength of collaboration) representing distinct parameters in the map. In maps, higher the relative link strength suggested stronger collaborative ties between units. Regarding pictorial depiction of geographical distribution of publications, iMapBuilder Interactive HTML5 Map Builder software was used.

Statistical analysis and ethics

Descriptive statistics were presented as frequencies and percentages. Mean, median, and range were presented for continuous data; the interquartile range (Q1-Q3) was presented in case of medians.

Microsoft Excel was used for data analysis and presentation. Since this study did not include any human data nor human subjects, and was based solely on electronic data, this study was exempted from ethical approval.

RESULTS

Description of retrieved literature

Making use of the filter tools in Scopus we selected research articles and reviews utilizing optogenetics in neuroscience between years 2010-2020. Based on the given search string and

Table 1: Key initial publications involved in making optogenetics a mainstay technique in Neuroscience.

Microbial Opsins		
Paper Highlights	**First Author/Journal/Year**	**Times Cited**
Rhodopsin-like Protein: *Halobacterium halobium*	(Dieter Oesterhelt, *Nature New Biology*, 1971)	1576
Rhodopsin-regulated calcium currents: *Chlamydomonas*	(Hartmann Harz, *Nature*, 1991)	188
Bacteriorhodopsin expressed in *S. pombe*	(Hildebrandt V, *Proc. Natl. Acad. Sci. U.S.A.*, 1993)	24
Functional expression of bacteriorhodopsin in oocytes	(Nagel G, *FEBS Lett.*, 1995)	66
Two rhodopsins: *Chlamydomonas reinhardtii*.	(Sineshchekov OA, *Proc. Natl. Acad. Sci. U.S.A.*, 2002)	408
Channelrhodopsin-1 (ChR1): A light-gated proton channel in green algae	(Nagel G, *Science*, 2002)	753
Channelrhodopsin-2 (ChR2): A directly light-gated cation-selective membrane channel	(Nagel G, *Proc. Natl. Acad. Sci. U.S.A.*, 2003)	1788
Red-shifted optogenetic excitation: *Volvox carteri*	(Zhang F, *Nat. Neurosci.*, 2008)	392
eNpHR: A Natronomonas halorhodopsin enhanced for optogenetic applications	(Viviane Gradinaru, *Brain Cell Biol.*, 2008)	350
Halorhodopsin: Improved expression and targeting	(Shengli Zhao, *Brain Cell Biol.*, 2008)	145
Channelrhodopsin-1 (ChR1) and-2 (ChR2): Molecular determinants	(Hongxia Wang, *J. Biol. Chem.*, 2009)	139
Engineered channel rhodopsin variants: Improved properties and kinetics	(John Y Lin, *Biophys. J.,* 2009)	479
Bi-stable channel rhodopsins: Modification at the C128 position	(André Berndt, *Nat. Neurosci.*, 2009)	418
Channelrhodopsin-2: Structural guidance of the photocycle	(Christian Bamann, *Biochemistry*, 2010)	163
Opsin expression-targeting genetic strategies		
Paper Highlights	**First Author**	**Times Cited**
Optical control of neural activity: Millisecond-timescale neural regulation	(Edward S Boyden, *Nat. Neurosci.*, 2005)	3087
Channelrhodopsin-2: Optical control of excitable cells	(Feng Zhang, *Nat. Methods*, 2006)	532
Channelrhodopsin-2 Transgenic mice: *In vivo* light-induced activation of neural circuitry	(Benjamin R Arenkiel, *Neuron*, 2007)	551
Channelrhodopsin-2 transgenic mice: High-speed mapping of synaptic connectivity	(H. Wang, *Proc. Natl. Acad. Sci.* U.S.A., 2007)	304
A FLEX switch targets channelrhodopsin-2 to multiple cell types	(Deniz Atasov, *J. Neurosci.*, 2008)	471
Parvalbumin neurons and gamma rhythms enhance cortical circuit performance	(Vikaas S Sohal, C5 2009)	1630
Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning	(Hsing-Chen Tsai, *Science*, 2009)	838
Activation of groups of excitatory neurons in spinal cord or hindbrain: locomotion	(Martin Hagglund Martin, *Nat. Neurosci.*, 2010)	190
Technological aspects: *In vivo/ Invitro* optics		
Paper Highlights	**First Author**	**Times Cited**
Next-Generation Optical Technologies: Illuminating genetically targeted brain circuits	(Karl Deisseroth, *J. Neurosci.*, 2006)	512

Microbial Opsins		
Targeting and Readout Strategies for Fast Optical Neural Control: *In vitro* and *in vivo*	(Viviana Gradinaru, *J. Neurosci.*, 2007)	372
Optogenetic control of hypocretin neurons: Neural substrates of awakening probed	(Adamantidis AR, *Nature*, 2007)	894
An optical neural interface: in vivo control of rodent motor cortex	(Alexander M Aravanis, *J. Neural Eng.*, 2007)	729
Sparse optical microstimulation in barrel cortex: Driving learned behaviour in freely moving mice	(Daniel Huber, *Nature*, 2008)	372
Optical deconstruction of parkinsonian neural circuitry	(Viviana Gradinaru, *Science*, 2009)	1106
Optogenetic interrogation of neural circuits: technology for probing mammalian brain structures	(Feng Zhang, *Nature Protocols*, 2010)	516
Closed-Loop and Activity-Guided Optogenetic Control	(Logan Grosnick, *Neuron*, 2015)	231

A

Language	Frequency	% (N = 2621)
English	2613	99.7
Russian	4	0.2
German	3	0.1
Chinese	1	0.04
Total	2621	100.0

B

Figure 1: A) Document number based on medium of language. B) The number of articles and reviews included in the bibliometric analysis.

filters used 2621 documents were retrieved. English was the predominant language used in these retrieved publications (2615; 99.7%) (Figure 1A). Majority of these publications were articles (2065; 79%), and the rest were reviews (556; 21%) (Figure 1B).

A total of 1,05,381 citations were obtained during the study period having a mean of 40.2 ± 10.9 citations per document, a range of 0-157, and a median (Q1-Q3) of 5 (2–9) citations per document. The *h*-index of the retrieved documents stood at 131 (Table 2).

Mapping of author keywords using VOSviewer revealed 5 main clusters containing 217 author keywords such as transgenic mice, brain slice, somatostation, pyramidal cells, parvalbumin, cytology, interneuron, neural inhibition, gabaergic neurons, interneurons etc. in cluster 1 (Red-80 items); striate cortex, somatosensory cortex, cerebral cortex, brain cortex, visual stimulation, vision, wakefulness, etc. in cluster 2 (Green 71 items); anxiety, amygdala, avoidance behavior, basolateral amygdala, classical conditioning, dopamine, reward, motivation, nucleus accumbens, reinforcement, animal behavior, learning, memory, prefrontal cortex, etc. in cluster 3 (Blue-62 items); animal model, knockout mouse and pathology in cluster 4 (Yellow-3 items); and finally cell activation in cluster 5 (Purple-1 item) (Figure 2).

Keywords with minimum occurrences of 50 times were shown in the map (217 keywords-5 clusters). Keywords having close spatial locations in the map have a higher chance of co-occurring together. For example, dopamine, dopaminergic nerve cell, motivation, reward, depression, odor, memory, learning, animal behavioral, anxiety, etc. occur close to each other in cluster 3 among 62 items signifying a close relationship and co-occurrence in documents (Note: "Optogenetics" with 1761 occurrences and a link strength of 39845 was removed from the analysis since it is the main component of the search term used).

Authorship pattern, collaboration, and prolific authors

In terms of total number of publications, Deisseroth, K. (*n* = 59); Boyden, E.S. (*n* = 26); Yamanaka, A. (*n* = 17); Kravitz, A.V. (*n* = 16); and Lee, J.H. (*n* = 16) were the top 5 authors utilizing optogenetics as a technique in Neuroscience (Table 3). The current affiliation and geographical location of the institutions of these the authors are mentioned in Table 3.

Using the VOSviewer software, top author collaborations in the field of optogenetics were mapped. The map included 56 authors-each represented by a circle-in 11 clusters (Figure 3).

In the collaborative author map (Figure 3), listed authors had a minimum of 10 publications and 100 citations. Adesnik H. and Lüthi A. were isolated as single author clusters whereas cluster 1, cluster 2 and cluster 3 had 11{chen x.; li b.; li h.; li x.; li y.; wang h.; wang l.; zhang j.; zhang x.; zhang y.; zhang z.}, 9{Augustine gj.; boyden e.s.; buzsaki g.; emiliani v,;

Feng g.; murphy t.h.; Svoboda k.; tye k.m.; zeng h.}, and 8{bonci a.; bruchas m.r.; de lecea l.; deisseroth k.; petersen c.c.h.; sohal v.s.; stuber g.d.; yizhar o.} authors respectively (Table 4). Deisseroth k. and Boyden e.s. are the top two authors with the highest total link strength signifying with these authors form different but connected hubs in the VOSviewer map (Figure 3; Table 4).

Table 2: Citation analysis by year of retrieved documents.

Year	Frequency	% *n* = 2621	Total Citations	Mean +/-SD of citations	Median (Q1-Q3) of citations
2010	21	0.8	2610	124.3 ± 15.4	5 (1-12)
2011	44	1.7	4264	96.9 ± 18.6	4 (1-11)
2012	91	3.5	7447	81.8 ± 14.4	4 (2-10)
2013	206	7.8	14138	68.6 ± 12.6	5 (2-11)
2014	211	8	12217	57.9 ± 9.8	5 (2-11)
2015	285	10.8	28240	99.1 ± 12.2	5 (2-10)
2016	286	10.9	9989	34.9 ± 8.8	4 (1-9)
2017	326	12.4	17080	52.4 ± 6.5	4 (1-9)
2018	382	14.6	6141	16.1 ± 7.0	1 (0-6)
2019	357	13.6	2575	7.2 ± 5.6	2 (0-5)
2020	412	15.7	680	1.7 ± 2.4	1 (0-2)
Total	2621	100	105381	40.2 ± 10.9	5 (2-9)

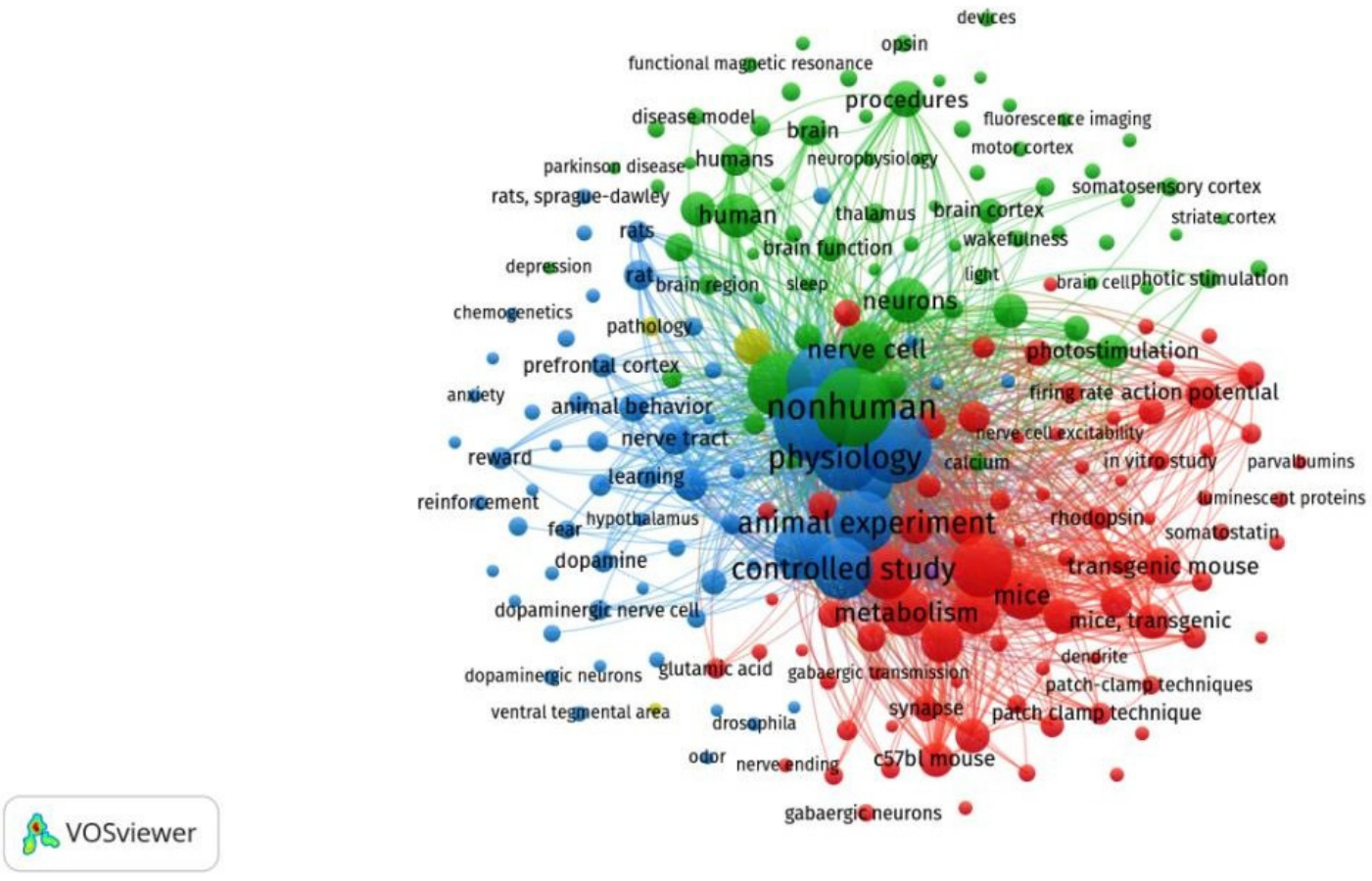

Figure 2: Network visualization map of author keywords occurrences (i.e. keywords listed by the author).

Stronger research collaborations are indicated by closely packed circles. Deisseroth, K. was the author with the highest total number of Links (L = 20), Total Link Strength (TLS = 31) and documents (N = 57). This was followed by Boyden, E.S (L = 9; TLS = 12; N = 25); Kravitz, A.V. (L = 5; TLS = 10; N = 16); Yamanaka, A. (L = 3; TLS = 9; N = 17); and Lee, J.H.(L = 4; TLS = 9; N = 16) as the top five collaborative authors having highest total link strength (Table 5).

Table 3: Top 10 authors in the field of Optogenetics in Neuroscience, their current affiliations and locations.

Ranking	Author name	Total document count	Current Affiliation	Country
1	Deisseroth, K.	59	Stanford University, Palo Alto	United States
2	Boyden, E.S.	26	Massachusetts Institute of Technology, Cambridge	United States
3	Yamanaka, A.	17	Nagoya University, Nagoya	Japan
4	Kravitz, A.V.	16	Washington University School of Medicine in St. Louis, St. Louis	United States
5	Lee, J.H.	16	LVIS Corporation, Palo Alto	United States
6	Murphy, T.H.	15	The University of British Columbia, Vancouver	Canada
7	Nestler, E.J.	15	Nash Family Department of Neuroscience and Friedman Brain Institute, New York, NY	United States
8	Stuber, G.D.	15	University of Washington, Seattle	United States
9	Buzsaki, G.	14	NYU Langone Health, New York	United States
10	Kreitzer, A.C.	14	University of California, San Francisco, San Francisco	United States

The oldest authors related to the optogenetics field in terms of when they published their first document was BuzsÃ¡ki, G. in 1973, Nestler, E.J. in1977, Murphy, T.H. in 1986, Deisseroth, K. in 1990, and Yamanaka, A. in 1997. Boyden, E.S.; Stuber, G.D.; Kreitzer, A.C. published their first document in 2000 which was followed by Lee, J.H. in 2002 and then Kravitz, A.V. in 2004 (Supplementary Table 1). The total publication count of Nestler, E.J. is the highest with 692 publications followed by Deisseroth, K. with 398 publications and BuzsÃ¡ki, G. with 390 publications. Among the top listed authors in the optogenetics field Nestler, E.J.; Deisseroth, K.; and BuzsÃ¡ki, G. have an h-index of 156, 135, and 132 respectively (Supplementary Table). In terms of total citation count, Nestler, E.J. and Deisseroth have a clear lead with 92273 and 68179 citations respectively over other authors in the field of optogenetics (Supplementary Table 1). The top cited article for each of the top 10 authors in optogenetics along with the year and journal of publication during the study time period is given in (Supplementary Table 1).

Top cited articles of the 10 most productive authors

The main article themes along with the key finding(s) and citation count of the top 10 cited articles for each of the top 10 authors are highlighted in Table 6. The top 10 cited articles were chosen for each author while reviews were excluded, as they do not contain original findings. The name of the first author, year of publication, title of article, journal, affiliation of first author, key points of article, and number of times cited are given in a supplementary excel document. The most cited articles for Deisseroth, K.(#1) within the study period include areas in optogenetic technological advancements (ChETA, Optetrodes), circuitry involved in depression, cognitive behaviors, aversion, countering seizures, reward-seeking behaviors and promotion of reward. Boyden, E.S.(#2) has his most cited in the optogenetics technological development sphere (Cre dependent optogenetic and intersectional targeting transgenic mice, high light sensitive optical neural silencer, Non-invasive optical inhibition-red shifted microbial rhodopsin, single cell resolution optogenetics) as well as circuitry involved in Slow Wave Sleep (SWS), primate visualmotor behavior, gamma and that a activity regulation, and optogenetic characterization of the temporal linearity of the MRI-BOLD response. Yamanaka, A.'s (#3) top 10 articles include articles related to top-down regulation of sensory perception, MCH neurons in sleep/wake regulation, glial based ischemic glutamate excitotoxicity, reversing pathological allodynia, NREM sleep regulation by VTA gabaergic neurons, aggressive behavior, top-down parasympathetic control, eNpHr2.0 Rosa 26 knock-in mice. Kravitz, A.V.'s (# 4) top 10 cited articles include striatal circuitry associated with reinforcement, activity induced dsDNA breaks exacerbated by B-amyloid, basal ganglia gating, in dentification of striatal projection neuron subtypes, D1 versus D2 Medium Spiny Neuron (MSN) downstream pathway mapping,

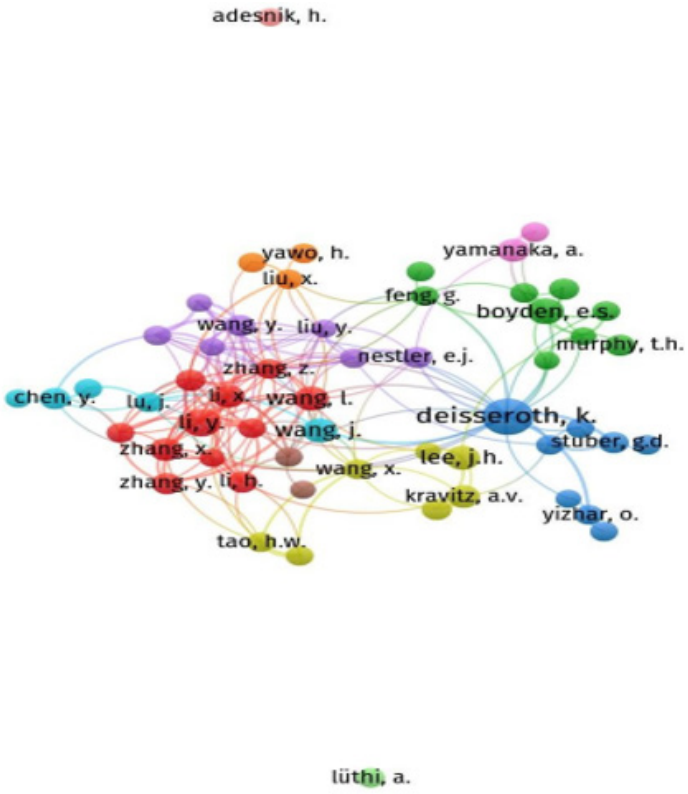

Figure 3: VOSviewer map view of collaborations between top authors in optogenetics: Authors with a minimum of 10 publications and 100 citations were visualized. The map included 56 authors in 11 clusters who met the criteria of being active authors. Some names are not seen due to overlap of names. Clusters indicate active authors of close research collaboration.

cell specific interventions for motor recovery in dopamine deleted mice, constraining reward seeking, striatopallidal regulation of avoidance behavior, and medial amygdala pathway in experience-dependent aggression escalation.

Lee, J.H.'s (# 5) articles include central thalamus regulation of cortical and subcortical networks, hippocampal dorsal versus ventral downstream connectivity using opto-fMRI, opto-fMRI to validate a multivariate dynamic systems model for causal brain interactions, brain circuit function using dynamic causal modeling for Opto-fMRI, to study brain circuit function, seizure-like after discharge mapping using simultaneous LFP and opto-fMRI, *in vivo* human stem cell graft into host neural circuits, high throughput opto-fMRI imaging, and fMRI analysis methods for heterogeneous BOLD responses.

Murphy, T.H.'s (# 6) top cited articles included distinct cortical circuits for motor maps and complex forelimb movement, GABA neuron regulation of cortical blood flow, network dynamics monitoring post stroke, cortical output motor remapping and functional recovery post spinal injury, prostaglandin mediated E2 neurovascular coupling, set-up for chronic light-based motor mapping, PV neuron stimulation-evoked network activity recovery post global ischemia-somatosensory cortex, widespread deficits in motor output post stroke, resistance of optogenetically evoked motor function to global ischemia and reperfusion, and mesoscale optical recordings to assess regional and functional connectivity. Nestler, E.J.'s (# 7) top cited articles included Antidepressant neuronal pathways-m PFC optogenetic stimulation, cocaine craving circuitry-Amygdala to NAc, PFC circuits in depression and anxiety-Cholecystokinin induced Delta Fos B, stimuli inducing Delta Fos B in MSNs, BDNF in mesolimbic reward pathway-gated by stress and CRF, chronic social-stress induced depressive behaviors, mapping brain metabolic connectivity with uPET and optogenetic stimulation, Mesolimbic BDNF mediating nociception in Chronic Neuropathic Pain, resilience to social stress in susceptible mice-alpha 1 and 2 Adrenergic pathways, and Orexin signaling in LHb modulating aggressive behavior in mice.

Stuber, G.D.'s (# 8) top cited articles include LH to LHb glutamatergic neurons regulating feeding and reward, medial preoptic area social reward circuit under hormonal control, LC to BLA noradrenergic anxiogenic circuit, inhibition of pre-synaptic GABA release in the BNST mediated by kappa opioid receptor signaling, vmPFC encoding of cocaine associated memory-temporal dynamics in recall and extinction, PVT projection neurons integrating signals for cue reward processing, inhibition of BLA to EC circuit disrupting acquisition of contextual fear, Local modulation of presynaptic release-DA terminals in the NAc, CeA neurotensin neurons in hedonistic behaviors, and optical suppression of drug-evoked phasic dopamine release. BuzsÃ¡ki, G.'s (# 9) top cited articles include precise motor movement regulation-inhibition of purkinje cell activity, tracing corticocortical connections between motor forelimb areas, BG inputs inducing excitatory motor signals in the thalamus, stimulation of inputs in LA forms associative fear memory, probing neuronal populations-combining micromirror based optogenetics and VSDI imaging, NAc D2 MSNs in cocaine induced behavioral sensitization *in-vivo* excitatory GABA loop, improved luminopsins, and optogenetics as a tool for assessing functional synapse formation in neuronal connections in co-culture systems. Kreitzer, A.C.'s (# 10) top cited articles include dendritic versus perisomatic inhibition regulating activity of hippocampal place cells, micro-LEDs on silicon neural probes-high resolution optogenetic studies, circuitry underlying hippocampal ripple formation, induction of theta resonance in cortical circuits, spatio-temporal control of mutiple neurons *in vivo*-diode probes, implantable neural probes-monolithically integrated dieletric waveguide and recording electrodes, unraveling behavioral correlates of hippocampal and mossy cells, hippocampal place map stabilization by SPW-Rs, circuit architecture and dynamics in hippocampal network.

Table 6 The following data of the top 10 authors and their top 10 highest cited articles in descending order was retrieved from SciVerse Scopus with the given search string and filters-See supplementary file for more information for each published

article. Reviews have not been considered, as these are not primary findings of an author, which this table intends to portray. Overlapping documents between authors, if any, have being mentioned only once with priority given to the more productive author in optogenetics)

Author collaborative clusters, citation clusters and highest cited document clusters

Neuroscience domain/area-wise VOSviewer constructed author collaborative and citation maps (top authors and highest cited documents) are displayed in Figure 4. The domains/areas in neuroscience represented in Figure 4 are domains in which optogenetics has made a significant contribution towards understand causal or associated circuitry. These represent the key research areas in neuroscience such as: Mood and Affective Behavior, Anxiety and Fear related Behaviors, Social behavioral states, Addictive and compulsive behavioral states, Motivational state (Reward versus risk), Cortical rhythms regulating Behavior, Learning and Memory, Epilepsy, Stroke and Neuro-degeneration. We ensured that authors that have significantly contributed to these areas (No. of publications in the area >= 3), and highly cited documents (No. of citations per document >= 50) are mapped using VOSviewer by setting appropriate thresholds. In any Vosviewer map, the size of the circles represent the weightage in the map, the thickness of the connecting links represents link strength, the distance between two spheres is inversely proportional to their closeness, and the units of a given cluster represent a closely connected group.

Preferred journals

Among the journals, the Journal of Neuroscience, Neuron, Nature Neuroscience and Elife were the preferred journals to publish articles using optogenetics as a technique. The journal of Neuroscience which is the official journal of the 'Society for Neuroscience' published 329(12.5%) documents, Neuron published 314 (12%) documents, Nature Neuroscience published 184 documents (7%), and Elife published 179 documents (6.8%) pertaining to Optogenetics.

Interestingly, these journals are top tier journals in the field of Neuroscience with Impact Factors (IF) 5.67 for 'Journal of Neuroscience', 14.415 for 'Neuron', 20.071 for 'Nature Neuroscience', 7.08 for 'Elife' and 3.156 for 'Frontiers in Neural Circuits'. This suggests that papers that include optogenetics as a technique to answer neuroscience-based research questions get published in high impact neuroscience journals. 'E-neuro' (2.9%), 'Journal of Neurophysiology' (2.9%), 'Frontiers in Cellular Neuroscience' (2.4%), 'Current Opinion In Neurobiology' (2.1%) and 'Journal of Visualized Experiments' (1,7%) are moderately popular with neuroscientists for publishing optogenetic related documents (Table 7).

Using VOSviewer, a co-citation map of journals publishing a minimum of 500 citations in optogenetics was constructed. Based on the map, 42 journals were clustered in 4 distinct groups: cluster 1: 17 journals, cluster 2: 16 journals, cluster 3: 8 journals, cluster 4: 1 Journals (Figure 3). The *'Journal of Neuroscience'* is most connected in terms of the number of lines it receives from other journals, indicating that this journal is most co-cited with other journals.

Furthermore, the journal of Neuroscience had the largest oval shape in the map indicating that this journal had the highest citation count in optogenetics (Figure 5).

In terms of total number of publications in the top 10 journals in the year 2020, '*Elife*' stood first at 5574, '*Journal of Visualized Experiments*' was in second with 5213 documents, and *'Journal of Neuroscience'* was third with 3561 documents (Supplementary Table 3). In keeping with the total publication count in 2020; *'Elife'* had the highest total citations count standing at 60, 463, followed by *'Journal of Neuroscience'* (37,553), *'Neuron'* (36,000), and *'Nature Neuroscience'* (25093) (Supplementary Table 3). The *h*-index of the top three journals in 2020 were 14, 21, and 22 respectively (Supplementary Table 3).

Interestingly articles relating to microglia and their functioning with a particular emphasis on signaling pathways associated with normal physiology and with disease conditions had the highest number of citations in the top three Neuroscience Journals in 2020. The articles titled, *"Microglia actively remodel adult hippocampal neurogenesis through the phagocytosis secretome"* in Journal of Neuroscience,

"TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge" in Neuron, and "*Lipid-droplet-accumulating microglia represent a dysfunctional and pro-inflammatory state in the aging brain*" in Nature Neuroscience had citations counts of 51, 64 and 85 respectively in 2020 (Supplementary Table 4).

Among the top 10 articles in optogenetics (Table 8), five of them were reviews and five were articles. The Neuron Primer titled, "Optogenetics in Neural Systems" received the highest number of citations standing at 1157 which was published in Neuron in 2011. In this Neuron primer, OferYizhar from the karlDeisseroth group introduces reliable and targetable single component tools to excite (i.e. cation channels: Blue-green fast excitatory-ChR2, ChIEF, ChRGR, ChETAs etc.; Yellow-red fast excitatory-VChR1, C1V1 etc.), inhibit (Chloride pump: yellow-Red eNpHR3.0; proton pump: green-yellow Arch/ArchT, eBRetc), biochemically modulate (i.e., 500 nm: G-protein signaling-Opto-b2AR, Opto-a1AR, Rh-CT(5-HT1A); 450 nm: c-AMP signaling-bPAC, BlaC) and activate/deactivate through on/off switches (ChR2-step function opsins (SFOs), VChR1-SFOs). Besides the optogenetic channel tools, the primer talks about *in vivo* targeting of these optogenetic tools while achieving specificity through cell type specific viral promoters and Cre-driver mouse lines. This

Table 4: Productive authors in collaborative clusters determined by VOSviewer mapping.

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Cluster 8	Cluster 9	Cluster 10	Cluster 11
Chen, x.	Augustine, g.j.	Bonci, a.	kravitz, a.v.	chen, l.	chen, y.	liu, s.	arenkiel, b.r.	tanaka, k.f.	adesnik, h.	lüthi, a.
Li, b.	Boyden, e.s.	Bruchas, m.r.	kreitzer, a.c.	chen, z.	lu, j.	liu, x.	lu, y.	yamanaka, a.	-	-
Li, h.	Buzsaki, g.	de lecea, l.	lee, j.h.	liu, y.	surmeier, d.j.	yawo, h.	-	-	-	-
Li, x.	Emiliani, v,	deisseroth, k.	liu, j.	nestler, e.j.	wang, f.	-	-	-	-	-
Li, y.	Feng, g.	petersen, c.c.h.	tao, h.w.	wang, s.	wang, j.	-	-	-	-	-
Wang, h.	Murphy, t.h.	sohal, v.s.	wang, x.	wang, y.	-	-	-	-	-	-
Wang, l.	Svoboda, K.	stuber, g.d.	zhang, l.i.	zhang, s.	-	-	-	-	-	-
Zhang,j.	Tye, K.m.	yizhar, o.	-	-	-	-	-	-		-
Zhang, x.	Zeng, h.	-	-	-	-	-	--	-	--	-
Zhang, y.	--	-	-	--	-	-	-	-	-	-
Zhang, z.	-	-	-	-	-	-	-	-	-	-

flexibility in targeting particular types of cells in heterogeneous population of cells in a brain region allows investigators to ask and answer very specific questions. This document discusses certain technical difficulties and limitations, along with future challenges in the optogenetic field (i.e areas related to light propagation in brain tissue, two-photon laser setups and Implantable Fiber-optic Lightguides (IFL) etc.) The second most cited review focuses on reward circuitry in the brain and how it is perturbed in mood disorders like depression.

Evidence portraying depression related changes to reward related circuits in humans and mice/rats at the cellular and molecular level (i.e gene expression and epigenetic changes) is presented. These maladaptive structural and molecular changes lead to depression induced synaptic plasticity. However of note is that depression susceptibility varies based on genetics with many studies hinting at genes involved in susceptibility to depression or resilience. Interestingly, this review highlights the fact that depression and reward/addictive circuitry are linked and overlap at key nodes. Thus, it is conceivable that changes in such linked circuitry lead to lack of pleasure/reward seeking and/or dulled value perception of reward which is associated with depression. The third most cited article in optogenetics generates and characterizes four Cre dependent knock-in genetically engineered mouse lines with Channel Rhodopsins (i.e., Ai27: ChR2H134R-tdTomato; Ai32: ChR2H134R-EYFP), halorhodopsin (Ai39: eNpHR3.0-EYFP) and Archaerhodopsin (Ai35: ss-Arch-EGFP-ER2). The creation of these cre dependent optogenetic reporter lines increased the feasibility and usability of optogenetics *in vivo* given the vast choice of readily available Cre driver lines. For example, investigators could pick cells types in the brain that they wished to optogenetically manipulate by crossing these reporter lines with a suitable Cre Driver line. The additional fluorescent labeling of opsin expressing cells visible and thereby easy to verify, experimentally manipulate, and observe in experimental setups. The review focusing on the neuronal circuits of fear and anxiety highlighted the achievements of optogenetics in identifying key neuronal circuitry associated with fear and anxiety. Optogenetics offers investigators spatial and temporal precision like never before thereby tremendously speeding up the discovery of circuitry related to fear and anxiety. Such reliable and precise optogenetic studies point to brain-wide neuronal networks connected by range projection pathways underlying fear and anxiety with local disinhibitory circuit gating as a common theme. Optogenetic studies show distinct but partially overlapping circuits involved in fear versus anxiety (e.g., Fear acquisition and expression: Basolateral Amygdala (BLA), central amygdala and the prelimbic region of the medial prefrontal cortex; anxiety: bed nucleus of the striaterminalis, the lateral septum, the Ventral Tegmental Area (VTA) and the BLA). Interestingly, optogenetic studies have shown that fear extinction involves distinct pathways in the same regions responsible for fear acquisition and expression, thereby implying that possible active cross-talk between these circuits may regulate the mechanism by which fear could be extinguished. Optogenetics allowed for detailed description of inhibitory neuronal type specific local afferent and efferent functional circuitry in the visual cortex. A combination of optogenetics and mapping techniques identified how different major subtypes of inhibitory neurons (i.e., parvalbumin, somatostatin and vasoactive intestinal peptide) talk to one-another and the output from such computations. Parvalbumin neurons strongly inhibit one another but don't connect much with

Table 5: Links (L), Total Link Strength (TLS), and Documents (N) of most productive authors.

Author Ranking	Author name	Cluster No	Links (L)	Total Link Strength (TLS)	Documents (N)
1	Deisseroth K.	3	20	31	57
2	Boyden E.S.	2	9	12	25
3	Yamanaka A.	9	3	9	17
4	Kravitz A.V.	4	5	10	16
5	Lee J.H.	4	4	9	20
6	Murphy T.H.	2	1	1	14
7	Nestler E.J.	5	6	9	15
8	Stuber G.D.	3	4	8	15
9	Buzsaki G.	2	3	3	14
10	Kreitzer A.C.	4	3	9	14

other neurons. In contrast, somatostatin interneurons inhibit all other interneuronal populations but not other somatostatin interneurons. VIP neurons preferentially inhibits somatostatin positive interneurons. In the article titled, "Evoked axonal oxytocin release in the central amygdala attenuates fear response" optogenetically stimulated hypothalamic oxytocin neuron terminals in the central Amygdala (CeA) caused fear suppression in fear conditioned rats. The lab from which optogenetics in neuronal systems originated-the Disseroth Lab-explained the scientific landscape over 10 years since its inception in the form of a historical Commentary titled, "Optogenetics: 10 years of microbial opsins in neuroscience." It details the conversion of optogenetics from a slow field possessing many technical hurdles for implementation to a rapidly growing and refined advanced neuronal perturbation technique (2010-2015), which has lead to many seminal discoveries of the underlying causal circuitry in certain functional outcomes and behaviors. The combination of optogenetics with previously discovered cell and tissue targeting strategies gave optogenetics an unmatched versatility. In the article by Alexxai V Kravitz *et al*., 2012 titled, "Distinct roles for direct and indirect pathway striatal neurons in reinforcement"; optogenetics was used to unravel specific effector pathways that are downstream of dopamine signaling. The authors show that preferential optogenetic activation of specific downstream dopamine pathways (i.e. D1 versus D2 pathways) could make the difference between induced persistent reinforcement or induced transient punishment. Thus, these circuits downstream of dopamine might be involved in encoding and expression of positive or negative valence associated with tasks that serve to guides future actions. The review by Kay M. Tye *et al*., 2012 titled," Optogenetic investigation of neural circuits underlying brain disease in animal models" highlights how optogenetics is the go to tool for delineating and obtaining a better understanding of underlying circuitry with a precision that was earlier not achievable earlier with the available techniques at that time. The topics covered in this review touched upon circuitry involved in basic behaviors and disease states. Optogenetics played a major role in furthering our understanding of microcircuits in the amygdala underlying fear and anxiety, the hippocampus and its mechanisms of recall of remote memory, misbalanced Excitation/ Inhibition and rhythmic oscillations regulated by interneurons in autism and schizophrenia, circuits encoding reward relevant to addiction, and the basic circuitry involved in neurological disorders and possible treatment strategies. The article titled, "Ultrafast optogenetic control" provides evidence of the technical millisecond temporal precision of ChR2 light induced spikes. However, there are limitations in terms of ChR2 inducing gamma spike sustained trains (important physiological frequency band) and artificially generating optically induced plateau potentials of 10mv (i.e., up-states) that could make interpretation difficult. This summarizes the most-cited seminal literature in the optogenetics field between years 2010-2020.

Geographical distribution of publications and Institutions

The 15 most productive institutions using optogenetics as a technique are listed in Table 9. The top three institutions are Howard Hughes Medical Institute (135 documents; 5.2%), Massachusetts Institute of Technology (118 documents, 4.5%) and Stanford University (112 documents, 4.3%). Out of the top 15 institutes, eleven institutes are situated in the United States of America, three institutions from Europe, and one institution form China.

Network visualization map of institutional collaborations (Figure 6). Institutions having published a minimum of 25 documents are shown in the map (41 institutions, 6 clusters). Institutions with the same color were commonly listed together as collaborative institutes. So, for example, Riken center for brain science, University of Tokyo, Massachusetts Institute of Technology, and Japan Science and Technology agency have the same color suggestive that these institutions collaborate with each other in the optogenetics space.

Table 6: Highlighting top 10 cited documents by top 10 most productive authors.

# 1: Deisseroth, Karl (6603640862)		
Article Theme	**Key Finding(s)**	**Times Cited**
Improved opsin: Ultrafast optogenetic control	ChETA.	496
Antidepressant therapy	Activation of mPFC.	408
Gamma rhythm and cognitive behavioral impairment	Activation of NR1R deleted PV neurons.	382
Conditioned Place Aversion (CPA)	Activation of GABA expressing VTA neurons.	364
Interrupting Seizures	Closed-loop inhibition of thalamic neurons connected to the stroke injured cortex.	355
Primate optogenetics	Tools (promoters, opsins, viral vector systems).	337
Increased motivation-based reward learning and behavioral flexibility	Increased phasic DA neuron activity.	236
Optrodes development	Simultaneous in vivo optical activation and recording.	233
Reward Signaling	Glutamatergic VTA to NAc signaling.	219
LHb output suppressed under rewarding conditions	Activation of VTA dopamine-GABA hybrid neurons targeting LHb pathway.	210
# 2: Boyden, Edward S. (35291447700)		
Article Theme	**Key Finding(s)**	**Times Cited**
Cre Dependent Optogenetic transgenic mice	Activation-(ChR2-td Tomato, ChR2-EYFP), Inhibtion-(halorhodopsin eNpHR3.0, archaerhodopsin Arch-ER2).	731
Intersectional mouse lines	Cre/Flp and Cre/Dre for intersectional targeting of neuronal sensors/effectors.	483
Increased sensitivity opsin (Arch T)	Three-fold increased sensitivity for neuronal inhibition over conventional Arch.	319
Red Shifted Opsin (JAWS)	Three-fold more sensitivity to red light; Non-invasive transcranial optical inhibition induced.	297
Slow Wave Sleep Induction	Silencing orexin/hypocretin hypothalamic neurons in inactive period.	171
Distinct Inhibitory regulation of gamma/theta rhythms on different time scales	Granule cells regulate gamma synchrony; glomerular cells regulate theta oscillations.	100
Temporally precise single-cell resolution optogenetics	Two-photon holographic connectivity mapping in slices using soma targeted CoChR.	99
Defective Monkey Visuomotor behavior (i.e., Saccadic eye movements)	Activation of Superior Colliculus neurons.	98
MRI BOLD optogenetic characterization	Mouse opto-Fmri showed that optogenetically locally induced neuronal activity drives BOLD (increased activity confirmed electro physiologically).	88

Slow Wave Sleep Induction and Increased wakefulness to sleep transitions	Chronic inhibition of orexin neurons (Arch-T) during active phase.	83

# 3: Yamanaka, Akihiro (55319368300)		
Article Theme	**key Finding(s)**	**Times Cited**
Accurate sensory perception	Top-Down Circuit M2-S1.	169
Sleep/wake regulation	Increased MCH activity-transition from NREM to REM sleep; MCH ablation-increased Wakefulness.	131
Ischemic excitotoxic glutamate induced brain damage	pH based regulation of astrocyte glutamate release.	112
Induction of slow wave sleep	Long lasting silencing of orexin/ hypocretin neurons.	81
State of wakefulness	Increased activity of LH orexin neurons.	30
Reversing pathological allodynia	Stimulation of VTA– NAc Pathway.	30
Regulation of NREM sleep	Increased VTA (GAD67)—LH (Orexin/ Hypocretin) promoted NREM sleep.	21
Aggressive behavior modulation	LH (Orexin)—LHb (GAD2); stimulation of LHb-GAD2 activity increases male-male aggression and reward in aggressive contexts.	17
Hypothalamic parasympathetic control of heart	Hypothalamic Orexin neurons control of cardiac vagal neurons in DMV.	13
Light induced neuronal silencing in knockin ROSA-26 mice	Microbial Halorhodopsin eNpHR 2.0.	8

# 4: Kravitz, Alexxai V. (6602759239)		
Article Theme	**Key Finding(s)**	**Times Cited**
D1 versus D2 pathways in reinforcement learning	Activation of D1 neurons: persistent reinforcement; Activation of D2 neurons: transient punishment.	566
Neuronal physiological activity leading to dsDNA breaks	Activity in Indirect pathway striatal neurons leads to expression of yH2A.X(i.e. DNA damage marker).	259
Basal ganglia output regulation	Activation of D1 direct MSNs inhibit SNr neurons-movement initiation; Activation of indirect D2 MSNs-motor suppression.	211
Optogenetic identification of striatal neurons	Distinct light-evoked spike properties (143 single units recorded-133 putative MSNs, 15 Putative FS interneurons).	58
Brain wide dissection of D1 versus D2 MSN downstream pathways	Opposing BOLD Responses in downstream regions correlated with single unit activity.	58
Motor recovery in dopamine deleted mice	Cell specific pallidal intervention (increased PV-GPe; decreased Lhx6-GPe activity rescues motor deficits).	44
Constraining reward seeking	Global Ventral Pallidum (VP) activity increase induces robust place preference; increased glutamatergic activity in VP induces place avoidance.	43

Feeding behavior	Increased activity of AgRP neurons in hypothalamus.	24
Approach-Avoidance behavior	Increased dorsolateral striato-pallidal iMSN neuron activity increase avoidance; decreased activity reduces avoidance.	11
Aggression Modulation (Effect of traumatic stress on aggression)	Increased activity of MeApv-VmH and MeApv-BNST leads to aggression priming.	5
# 5: Lee, Jin Hyung (57196135833)		
Article Theme	**Key Finding(s)**	**Times Cited**
Central thalamus arousal regulation	High frequency thalamic stimulation-arousal; whereas low frequency-behavioral arrest.	68
Dorsal vs. Ventral hippocampal connectivity	Stimulation of Intermediate Hippocampus-widespread cortical and sub-cortical activation; Stimulation of Dorsal Hippocampus-activation restricted to hippocampus.	50
Establishing causal brain interactions-Multivariate dynamic systems model	Optogenetic fMRI to validate computational causal interaction estimating methods.	29
Dynamic causal modeling for systems level circuit interactions and Neuromodulatory therapies	Validated by Optogenetic fMRI data in basal ganglia-thalamocortical network.	27
Seizure like after-discharges	Distinct recruitment of brain networks (measured by LFPs and fMRI) by after-discharges versus sub-threshold hippocampal stimulation using carbon based optrodes.	25
Connectivity of human stem cell graft with host neural circuits	Novel Opto-fMRI imaging platform to study graft-host connectivity.	21
Efficient real-time interactive high-throughput Opto-MRI imaging with parallel computation	1.7% of TR.	22
Opto-fMRI	Enabling causal tracing of activities arising from defined cell types and firing patterns across the whole brain.	17
fMRI analysis methods for heterogeneous BOLD responses	General Linear Model (GLM) inferior to gamma basis set and Fourier basis sets.	11
Opto-fMRI	Non-invasive method to measure global dynamic response (BOLD) to optogenetic stimulation of specific neural circuits.	9
# 6:Murphy, Timothy H. 7401632487		
Article Theme	**Key Finding(s)**	**Times Cited**
Complex forelimb movements	Through intra-cortical synaptic transmission while topography of motor maps via segregated outputs.	93
Regulation of blood flow by GABAergic neuron activity	Increased GABA neuronal activity leads to increased blood flow independent of net neuronal activity.	59

Optical mapping of network dynamics post stroke	Network wide downscaling and recovery after stroke different for peri-infact and surrounding non-affected regions.	58
Re-establishment of cortical motor maps after spinal cord injury	Pivotal role of minor dorsolateral corticospinal pathway in mediating spontaneous motor recovery.	57
Molecular mediators in neurovascular coupling (NVC)	COX2 Prostaglandin E2 regulates NVC through vasodilatory EP2, EP4 receptors.	48
Chronic light-based motor mapping	Light pulses of 2 mW produced well-defined stable maps; useful strategy to assess cortical reorganization or sensory-motor integration.	25
Prolonged Parvalbumin (PV) Network deficits in Somatosensory cortex post global Ischemia	PV neuron excitability reversed quicker than stimulation-evoked GABAergic synaptic network activity.	21
Assessment of excitability and motor output after Ministrokes	Wide-spread deficits in motor output despite recovery of cortical neuron excitability.	19
Differential sensitivity of sensory and motor systems to global Ischemia.	Motor output recovers faster than sensory systems.	10
Optical recordings to assess regional functional connectivity.	Channel rhodopsin and voltage-sensitive dye imaging.	9
# 7: Nestler, Eric J. 7102006227		
Article Theme	**Key Finding(s)**	**Times Cited**
Anti-depressent effect	Optogenetic stimulation of the medial prefrontal cortex.	410
Incubation of cocaine craving	Unsilencing of amygdala-accumbens synapses as withdrawal period increased.	191
Blockade of Cholecystokinin (CCK) mediated social defeat stress(Δ FosB)	Stimulation of cortico-amygdala blocks anxiogenic effect; stimulation of cortico-accumbens blocks social avoidance defects.	178
Δ FosB induction in striatal medium spiny neurons	By pharmacological, emotional and optogenetic stimuli (limbic brain regions to Nucleus Accumbens).	156
CRF and Stress gate BDNF in Nucleus Accumbens (NAc)-A stress context detecting function	Stimulation of Mesolimbic pathway increases BDNF in socially stressed mice but not naïve mice.	135
Chronic Social Stress-Induced depressive behaviors	Essential role of mesolimbic (VTA-NAc) BDNF Trk B signaling.	46
Brain metabolic connectivity mapping in awake rats	ChR2 stimulation with uPET recording of brain glucose metabolism.	46
BDNF in mesolimbic reward circuitry mediates nociception	Inhibiting VTA-NAc and decreasing BDNF signaling in NAc reverses Chronic Constrictive Injury (CCI) induced thermal hyperalgesia.	37

Resilience to social stress	Stimulation of LC-VTA signaling reverses depression related behavior in susceptible mice dependent on α1 and B3A adrenergic receptors.	18
Male aggressive behavior	Increased stimulation of the LH (orexin)-LHb(GAD2) leads to inhibitory tone in LHb and male-male aggressive behavior.	18
#8: Stuber, Garret D. 700714214		
Article Theme	**Key Finding(s)**	**Times Cited**
LH-LHb circuit for regulation feeding and Reward	Stimulation of glutamaertergic LHA-LHb leads to avoidance behaviors; Inhibition of LHA-LHb leads to real time place preference; LHA neurons bidirectionally regulate feeding.	150
Socially engaged reward circuitry	Stimulation of mPOA to VTA steroid responsive neurotensin expressing neurons promotes rewarding phenotypes, social approach and striatal dopamine release.	119
Anxiety-like behavior	Stimulation of LC-BLA Noradrenergic projection increases anxiety and aversive behaviors through B-adrenergicr receptors.	101
KOR (Kappa Opiod Receptors) role in CeA-BNST stress response	Long range GABAergic CeA-BNST connections inhibited by KOR activation.	99
VmPFC in extinction and recall of cocaine associated memory-reorganization over time	Stimulation of VmPFC facilitated extinction of remote memory; inhibition of VmPFC impaired recall of recent memory.	56
Reward seeking behavior	Disrupting Paraventricular Thalamus (PVT) coding of reward predicting cues leading to abnormal behavioral cue discrimination.	50
Contextual fear-memory	Inhibiting the BLA-EC circuit during acquisition lead to a significant lowering in freezing in context re-exposure.	47
Local modulation of synaptic release	Differential synaptic mechanisms of optogenetic versus electrical stimulation of dopamine release in the NAc.	42
Consumption of ethanol and palatable food-sweet fluids	Stimulation of the Central Amygdala (Neurotensin positive) to Parabranchial Nucleus leads to reinforcement and increase of ethanol/saccharin consumption in non-dependent animals.	23
Suppressing dopamine transients in drug associated behaviors	Inhibition of VTA NpHR expressing neurons reduced frequency of dopamine transients.	15

# 9: Augustine, George J. 55663195000		
Article Theme	**Key Finding(s)**	**Times Cited**
Precise control of movement kinematics	Suppression of spontaneous activity of Purkinje cells is sufficient for discrete control over movements.	135
Generation of new lines of optogenetic based transgenic mice	Enhanced halorhodopsin, better versions of channelrhodopsin, Florescent tags, and neuron specific promoters.	48
Optogenetic tracing of corticocortical connections invivo (Motor Forelimb areas)	Determining functional connectivity between RFA and CFA.	39
Basal Ganglia (BG) inhibitory input drives motor signals in thalamus	Stimulation of GP-BG input leads to surge of APs in VL neurons and post-inhibitory muscle contraction.	38
Associative fear memories	Stimulation of presynaptic input (main auditory brain regions) into Lateral Amygdala with accompanied foot shock was sufficient to serve as conditioned stimuli and increase freezing response.	32
Probing functions of neuronal populations	Micromirror based presynaptic stimulation(cerebellar Interneurons) with post synaptic VSD (purkinje neurons) imaging.	25
Cocaine induced behavioral sensitization	Stimulation of NAc D2R-MSNs attenuated expression of cocaine induced behavioral sensitization.	20
Excitatory GABA loop operating invivo	Stimulation of Parallel fibers(PF) leads to PF excitation via GABA A receptors in cerebellar molecular layer.	18
Luciferase opsin combinations for improved luminopsins	Genetically encoded means of manipulating neuronal activity via chemogenetics and optogenetics (LMO4 and iLMO4).	17
Approach for assessing formation of neuronal connections in hybrid co-culture systems	Stimulation of rat cortical neurons leads to increase in frequency of currents in IPSC derived human neurons.	14
# 10: Buzsaki, György 7006676856		
Article Theme	**Key Finding(s)**	**Times Cited**
Dissecting perisomatic and dendritic inhibition of hippocampal place cell activity	Inhibiting SOM interneurons increased burst firing; Inhibiting PV interneurons shifted theta spikes to the trough phase.	353
Monolithical tool for cellular circuit level analysis with spatiotemporal precision in freely moving animals	Four shank silicon probes consisting of 12 μLEDs and 32 recording sites.	214
Hippocampal ripple oscillations	Temporally precise local pyramidal cell-interneuron interactions support ripple generation.	192
Inhibition induced theta band spiking	Role of PV cells and Ih Channels in post inhibitory spiking of pyramidal cells.	173

Diode probes for spatiotemporal optical control of multiple neurons	Concurrent circuit monitoring and multisite perturbations.	158
Neural probe with monolithically integrated electrodes and waveguide	Optical targeting of single neurons with minimal power and monitoring with single unit recordings.	130
Granule cell-mossy cell interactions for pattern separation	Granule cells-sparse firing and single place field; Mossy cells-more active, multiple place fields and remapped under similar conditions.	104
Hippocampal pyramidal cell-interneuron circuitry and functional dynamics	Interneuron architecture and dynamics: Divergent synaptic connections-synchrony between interneurons; synchrony of convergent presynaptic inputs boosted postsynaptic drive; Spike transmission modulated by spike timing of post-synaptic cell.	72
Stabilizing hippocampal spatial maps	Scrambling sharp-wave ripples of place cells during learning caused remapping and no updating of spatial information.	71

In terms of country productivity, the United States of America has the highest productivity with 1715 documents (46.15%) (Table 10). The countries that have productivity above 100 documents are: Germany (249; 6.8%), Japan (195; 5.3%), China (193; 5.2%), United Kingdom (181; 4.9%), Canada (174; 4.7), France (141; 3.8) and Switzerland (113; 3.1).

A heat-map portraying this distribution is shown in Figure 7.

The dark maroon colour indicates the United States which is the major contributor of published Literature on optogenetics (>15% of total published documents). The lighter the shade the lower the contribution of documents from that country. The countries with no filled in color shows negligible or no contribution at all to published Literature in optogenetics (< 0.1%). Among the South Asian countries, Australia ranks first with 51 documents, followed by Singapore (27), India (15), New Zealand (14), Taiwan (10), Hong Kong (7), Thailand (3), Pakistan (2) and Bangladesh (1). In the African continent, South Africa is the only contributor to documents related to optogenetics (4). In South America, the top three productive countries are Mexico (16), Denmark (15), and Chile (10).

The thickness of connecting line between any two countries indicates strength of collaboration. For example, the link strength (collaboration) between USA and Germany was 84 and it represents a thick line. On the other hand, the line between USA and New Zealand had weak link strength of 1. Countries with similar color form one cluster. For example, countries with red color such as Spain, Austria, Hungary, Portugal, and Japan existed in one cluster and had the highest percentage of collaboration within this cluster (6 clusters; 24 items).

China, Canada, and Israel were clustered in yellow since the bulk of their collaboration is with the USA, so they are grouped with USA (Figure 8). In terms of cross-country collaborations, USA and germany had the highest link strength (i.e., 84), followed by USA and United Kingdom (i.e., 68), USA and China (i.e., 66), USA and Japan (i.e., 65), USA and Canada (i.e., 59). On the other hand, there are countries that were relatively spaced out in the map and had fewer thin connecting lines with other countries signifying weak collaborations between them (e.g., Argentina: Total Link Strength = 11, Documents = 14; and New Zealand Total Link Strength = 9, Documents = 11).

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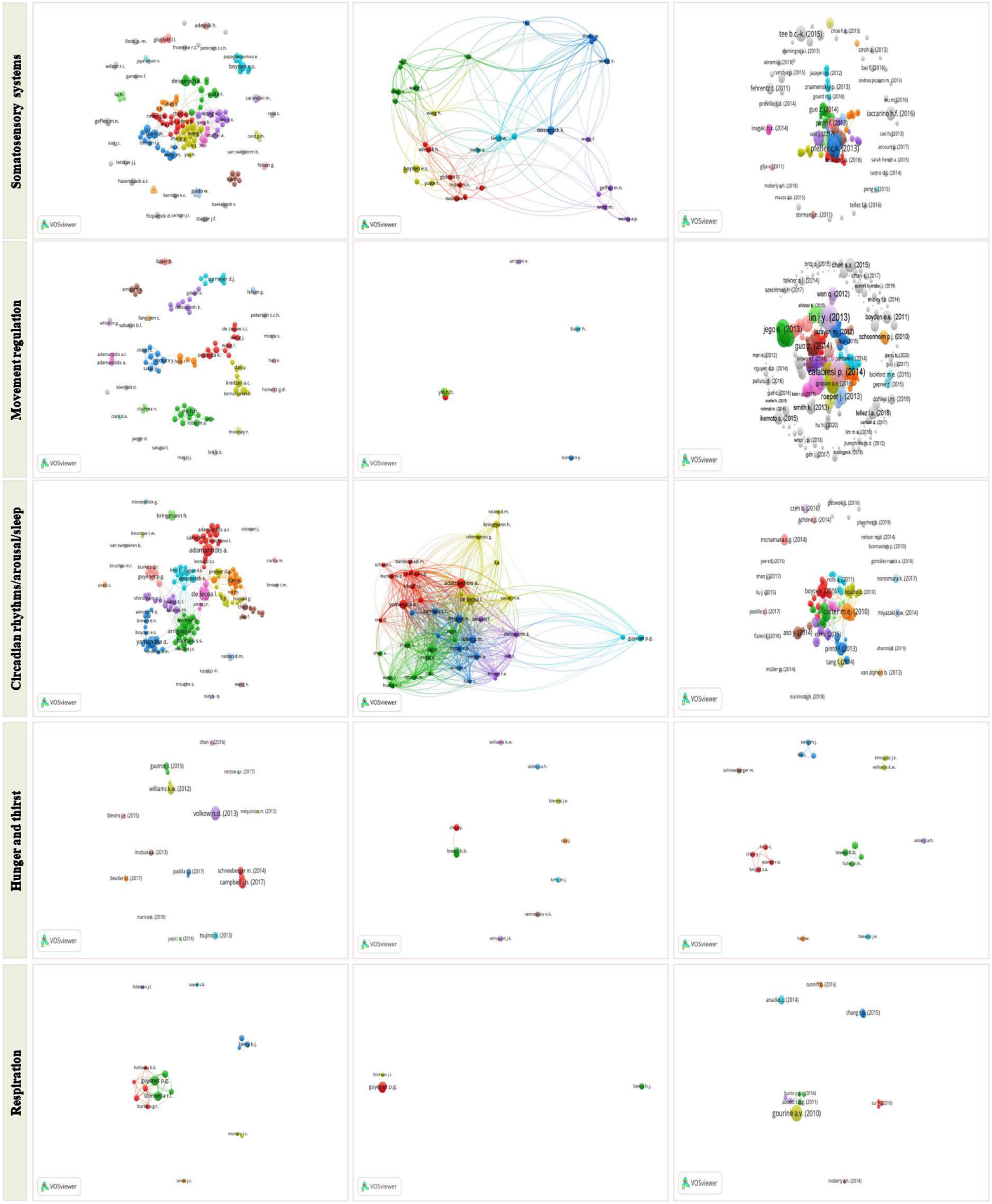
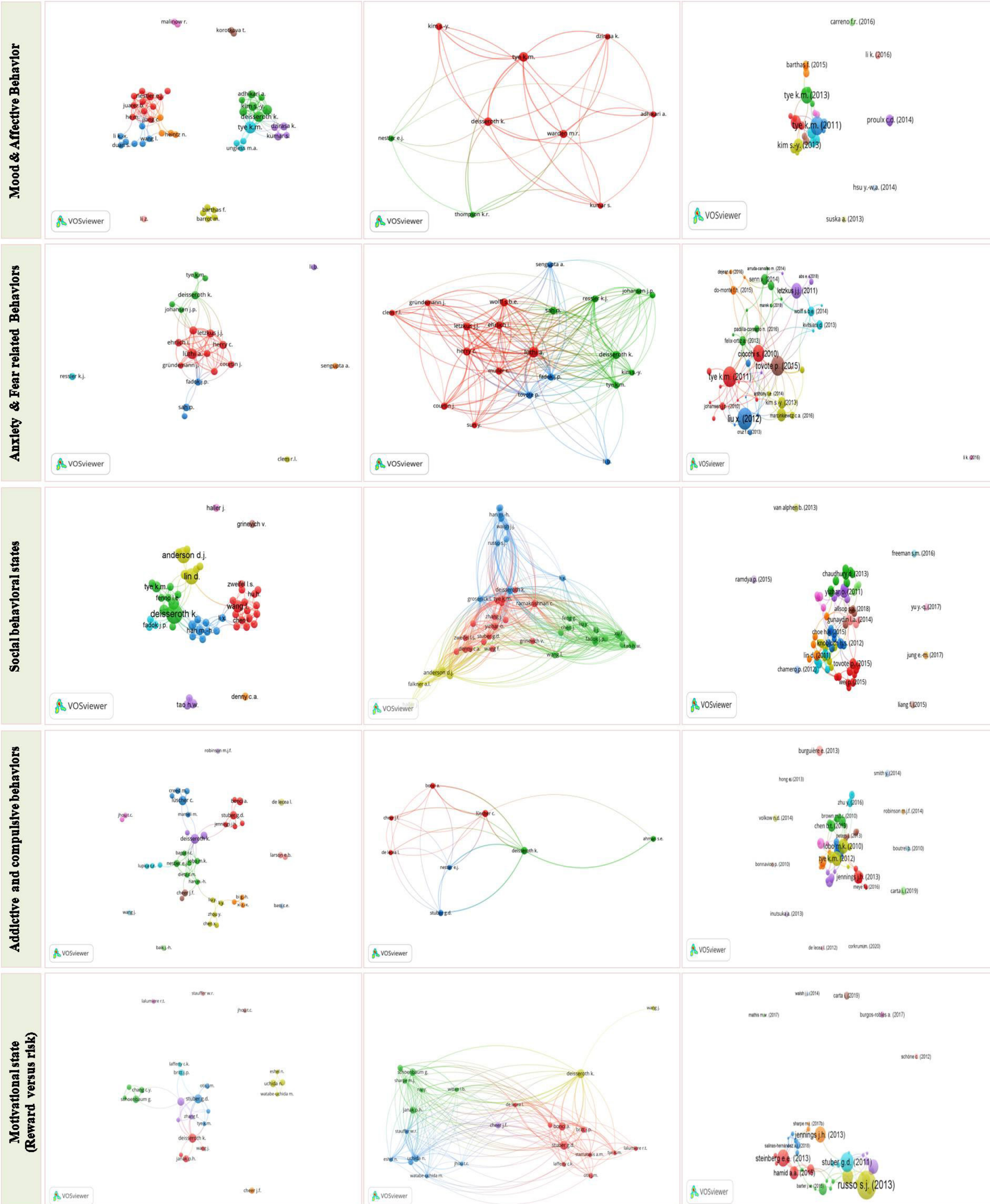
Growth of publications

The number of published documents applying optogenetics as a discovery-based tool increased year-on-year from year 2010-20 (Table 11). However, between the years 2010-13 there was a dramatic increase in the number of reviews and articles. During the years 2013-20, it increased gradually as is seen from the numbers. The year 2020 had the highest total number of documents with optogenetics (i.e. 412 documents) whereas 2010 had the lowest number of documents (i.e., 21 documents) (Table 11). A similar trend was seen in the number of citations that were obtained year-wise.


Somatosensory systems
Movement regulation
Circadian rhythms/arousal/sleep
Hunger and thirst
Respiration
VOSviewer


Mood & Affective Behavior
Anxiety & Fear related Behaviors
Social behavioral states
Addictive and compulsive behaviors
Motivational state (Reward versus risk)
VOSviewer
tye k.m.
deisseroth k.
anderson d.j.
lin d.
tye k.m. (2011)
tye k.m. (2013)
kim s.-y. (2013)
liu x. (2012)
tovote p. (2015)
ciocchi s. (2010)
letzkus j.j. (2011)
russo s.j. (2013)
stuber g.d. (2011)
steinberg e.e. (2013)
jennings j.h. (2013)
hamid a.a. (2016)

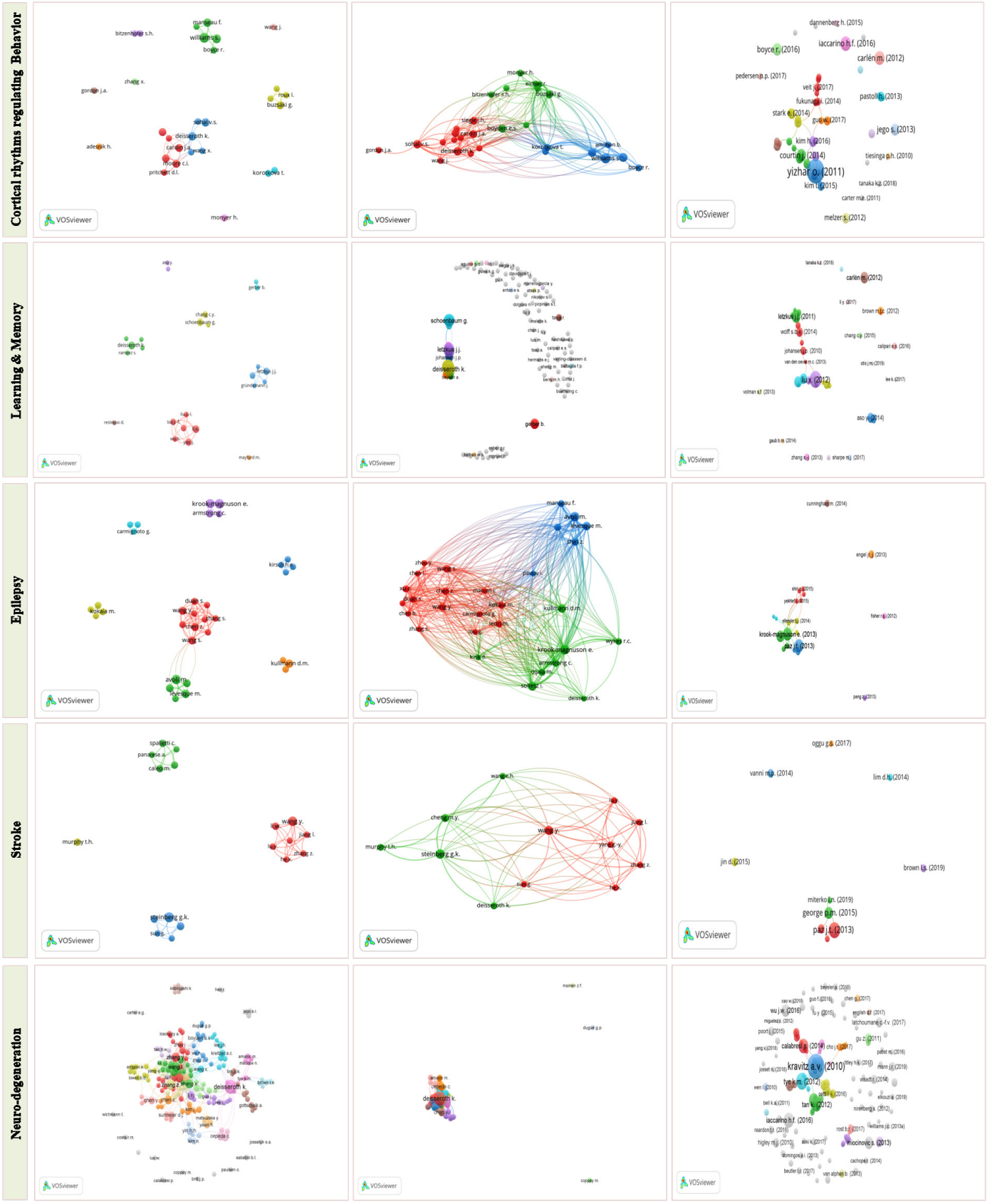


Figure 4: VOSviewer mapping based on top-author collaborations, top-citation clusters, and top-cited document clusters (i.e., documents consisting of articles and reviews) for different researched domains in Neuroscience using optogenetics: The left panel depicts author collaborative clusters, middle panel depicts citation based author clustering, and the right panel depicts citation based top-cited document clustering. Objects belonging to the same cluster in these maps are represented by the same color.

Table 7: The journals that have published more than 30 documents in optogenetics.

Journal	Number of documents	Percentage of Documents (%)
Journal of Neuroscience	329	12.6
Neuron	314	12.0
Nature Neuroscience	184	7.0
Elife	179	6.8
Frontiers in Neural Circuits	85	3.2
Eneuro	75	2.9
Journal of Neurophysiology	75	2.9
Frontiers in Cellular Neuroscience	62	2.4
Current Opinion in Neurobiology	55	2.1
Journal of Visualized Experiments	46	1.8
Frontiers in Neuroscience	45	1.7
Cerebral Cortex	44	1.7
Journal of Neuroscience Methods	44	1.7
Neuroscience	37	1.4
Frontiers in Behavioral Neuroscience	36	1.4
Journal of Neural Engineering	35	1.3
European Journal of Neuroscience	34	1.3
Neurophotonics	32	1.2

The citation count almost doubled each year in the first few years post 2010, but then fluctuated between years 2013 to 2020 (Table 2). The highest citation count during the study period was in 2015 (i.e., 28240 citations); the lowest citation count was in the year 2020 (i.e., 680 citations). Interestingly, the number of citations was on the decline post 2018 (17080 in 2017 to 6141 in 2018 to 2575 in 2019 to 680 in 2020). The mean number of citations per document in general showed a decreasing trend between years 2010-20.

However, there was a precipitous drop between the years 2015 to 2016 (i.e., 99 to 35 citations per document) and between years 2017 to 2018 (i.e., 52 to 16 citations per document). The inter-quartile range (Q1-Q3) and the median number of citations for each year are mentioned in Table 2.

With regards to the statistics based on authors and authorship, the total number of authors increased from 86 in years 2010 to 3244 in year 2020 (Table 12). During the study period a total of 15937 authors contributed to this work (Table 12). There was an exponential increase in the number of authors contributing to documents in the initial years (i.e., 2010-2013), post which there was a steady increase in the number of documents (Table 12). The average number of authors per document increased from around 4 (2010) authors per document to around 8 authors per document (2020) (Table 12). This indicates that on an average the number of authors per document doubled during the study period (Table 12).

A study of growth rate indicated that the Average Growth Rate (AGR) fluctuated between-0.1 to 1.1 (Table 13). The Relative Growth Rate (RGR) declined from 1.1 to 0.2 during the study period (Table 13). The RGR was 1.1 in 2011, steadily decreased to 0.4 in 2015; and then steadied at 0.2 between years 2018-2020 (Table 13). An analysis of the Doubling Time (DT) revealed an increase from 0.6 in 2011 to 4.1 in 2020. There was an instance of a rapid increase in DT during the study period (i.e., between 2013 to 2014, DT values of 0.8 to 1.5). Since the values of RGR and DT were not stable during the study period, this indicated that the growth in publications was not exponential (Table 13). The number of single author publications fluctuated throughout the study period while the percentage of single author publications declined in general (2010: 6; 28.6–2020: 0; 0) (Table 14). As a corollary, the number and percentage of multi-author publications increased during the study period (2010: 15; 71.4–2020: 412; 100) (Table 14). The collaborative index increased from 5.3 in 2010 to 7.9 in 2020 (Table 14). The degree of research collaboration among the authors of papers using optogenetics was 92.8%.

DISCUSSION

Bibliometric indicators of literature pertaining to the technique 'optogenetics' in neuroscience were sought after in this study. Since the United States of America is the most productive country in terms of document count, it is but natural that the predominant language contained in these documents is English. Even though countries and institutions in Europe were substantial contributors, majority of the documents using optogenetics were published in English. One possibility could be that high impact neuroscience journals that publish optogenetic based literature accept articles only in English. This would be best to cater to their wide neuroscience readership base arising from many countries.

The total number of publications (i.e., publication count) as well as the total citation count increased over the study period which can be attributed to the increasing number of labs/and investigators incorporating optogenetics into their respective research hypothesis and questions, especially between 2010-15.[21,36,37] The increasing total citation count might be attributed to the effectiveness of optogenetics as a potent discovery tool opening the doors to further important testable questions and hypothesis.[39,40] Thus, future neuroscience based studies building upon these fundamental discovery based papers

Table 8: Top 10 cited documents in optogenetics.

Rank	Title	Year	Journal name	Cited By	Type of document
1	Optogenetics in Neural Systems	2011	Neuron	1157	Review
2	The brain reward circuitry in mood disorders	2013	Nature Reviews Neuroscience	861	Review
3	A toolbox of Cre-dependent optogenetic transgenic mice for light-induced activation and silencing	2012	Nature Neuroscience	690	Article
4	Neuronal circuits for fear and anxiety	2015	Nature Reviews Neuroscience	641	Review
5	Inhibition of inhibition in visual cortex: The logic of connections between molecularly distinct interneurons	2013	Nature Neuroscience	600	Article
6	Evoked axonal oxytocin release in the central amygdala attenuates fear response	2012	Neuron	561	Article
7	Optogenetics: 10 years of microbial opsins in neuroscience	2015	Nature Neuroscience	537	Review
8	Distinct roles for direct and indirect pathway striatal neurons in reinforcement	2012	Nature Neuroscience	533	Article
9	Optogenetic investigation of neural circuits underlying brain disease in animal models	2012	Nature Reviews Neuroscience	499	Review
10	Ultrafast optogenetic control	2010	Nature Neuroscience	480	Article

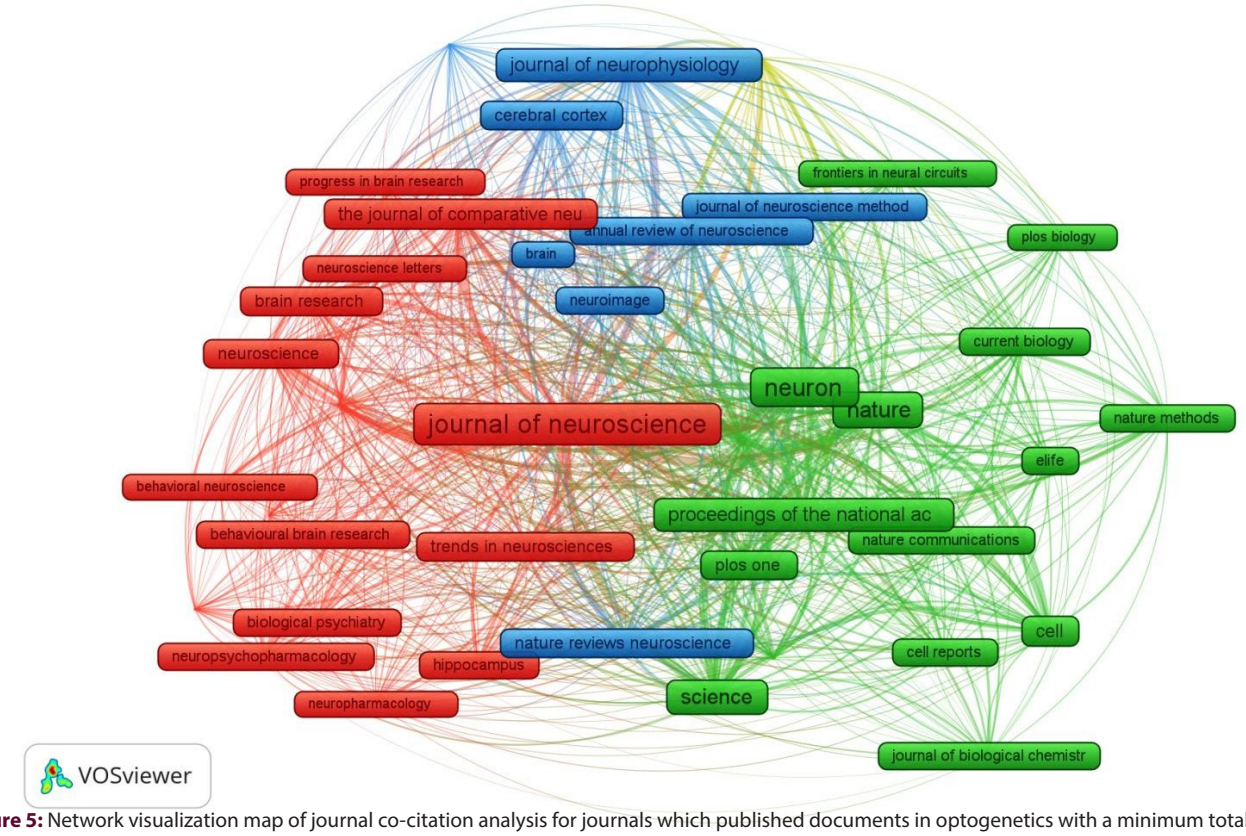


Figure 5: Network visualization map of journal co-citation analysis for journals which published documents in optogenetics with a minimum total of 500 citations. The Journal of Neuroscience one had many connecting lines with various journals indicating that this journal is being co-cited with various journals. Journals in the same cluster with the same color are being commonly co-cited together (42 journals; 4 clusters).

Table 9: The most productive institutes using optogenetics in neuroscience.

Affiliation	Number of Publications (N)	Percentage of Publications (%)
Howard Hughes Medical Institute	135	5.2
Massachusetts Institute of Technology	118	4.5
Stanford University	112	4.3
Harvard Medical School	111	4.2
CNRS Centre National de la Recherche Scientifique	82	3.1
National Institutes of Health NIH	81	3.1
Inserm	78	3.0
University of California, San Francisco	73	2.8
McGovern Institute	72	2.7
Columbia University	71	2.7
Chinese Academy of Sciences	57	2.2
University of Pittsburgh	49	1.9
University College London	49	1.9
Howard Hughes Medical Institute Janelia Farm Research Campus	47	1.8
University of California, Berkeley	46	1.8

would lead to their citation count increasing over time. From year 2015-2020, the total number of citations has dropped even though the total number of publications has increased. This could be attributed to recent studies not having adequate time to be cited as well as the plateauing of the number of papers in the second half of the study period (i.e., drastic decrease in citation count per article).

From the data, the average number of authors per document as well as the Collaborative Index (CI) kept on increasing throughout the course of the study period. This shows that optogenetics served as a favorable discovery-based tool for an increasing number of neuroscientists around the world. This was facilitated by the outstanding foundational contributions of Karl Diesseroth's and Ed Boyden's research clusters in the field of optogenetics.[40-42] These research groups transformed optogenetics from a hard-to-apply to a much easier and adaptable tool for neuroscience based research. Moreover, these discovered optogenetic tools were made easily available and widely accessible through viral repositories (e.g., Viral Vector Cores etc. for neurotrophic viruses containing opsingenes), mouse cores (e.g., Jax Lab for transgenic mice encoding opsin genes) as well as by training in the design, fabrication and usage of *in vivo* implantable optic fibers and probes (e.g., optrodes). Due to these initiatives promoting the dissemination of optogenetics around the globe, the total number of authors, the average number of authors per document, the degree of collaboration, and the collaborative index showed an increasing trend throughout the study period.

From data regarding the most productive authors and mapping of author clusters, Karl diesseroth is the most productive author with the most collaborative strength in the field of optogenetics. A second most productive author was his student Edward S. Boyden, having the second largest link strength. Not surprising, both authors were pioneers in the field of optogenetics providing evidence of the applicability of optogenetics as a tool in neuroscience in a seminal 2005 paper.[40] More importantly, these two authors and their research clusters were instrumental in making optogenetics a mainstay technique in neuroscience for establishing casual underlying neural circuitry in behavioral/physiological/disease states. However, one must not discredit the contributions of authors that formed the foundations for Eward S. Boyden's critical experiments in 2005, without which optogenetics in neuroscience would not have been possible.[43-49] Based on these game-changing findings by Eward S. Boyden and Karl Diesseroth, scientists of different nationalities and laboratories formed their research clusters and started to work together using optogenetics as a discover tool in their respective domains in neuroscience.[50-52] In keeping with this geographical spread, we see clusters of American, Asian, and European authors which either directly or indirectly linked up with Ed Boyden and Karl diesseroth.[21,23,53] In certain instances, scientists that were initially a part of the same research group in a particular lab using optogenetics, then moved on to start their own labs in different countries which contributed in a way to the spread of optogenetics as a technique across the globe.[54-56]

The USA ranked first in terms of number of neuroscience documents possessing optogenetics, in keeping with it being the country that houses most of the major institutions and authors contributing to optogenetic based neuroscience research (11 out of the 15 top institutions, and 8 out of the 10 top authors). Harvard Hughes Medical Institute (HHMI) is the major contributing institution signifying that optogenetics is used by an elite successful class of neuroscientists testing cutting edge ideas and hypotheses in Neuroscience. HHMI is followed by Massachusetts Institute of technology and Standford University in terms of institute productivity. In consonance with institutional productivity, Karl Deisseroth's lab is in Standford University, and Edward Boyden's lab is in Massachusetts Institute of Technology; both authors are currently HHMI funded. Interestingly, the HHMI funds scientists (based on their high quality of research and discovery), and not projects. With the money awarded to them, these scientists are thus able to spend the money on asking

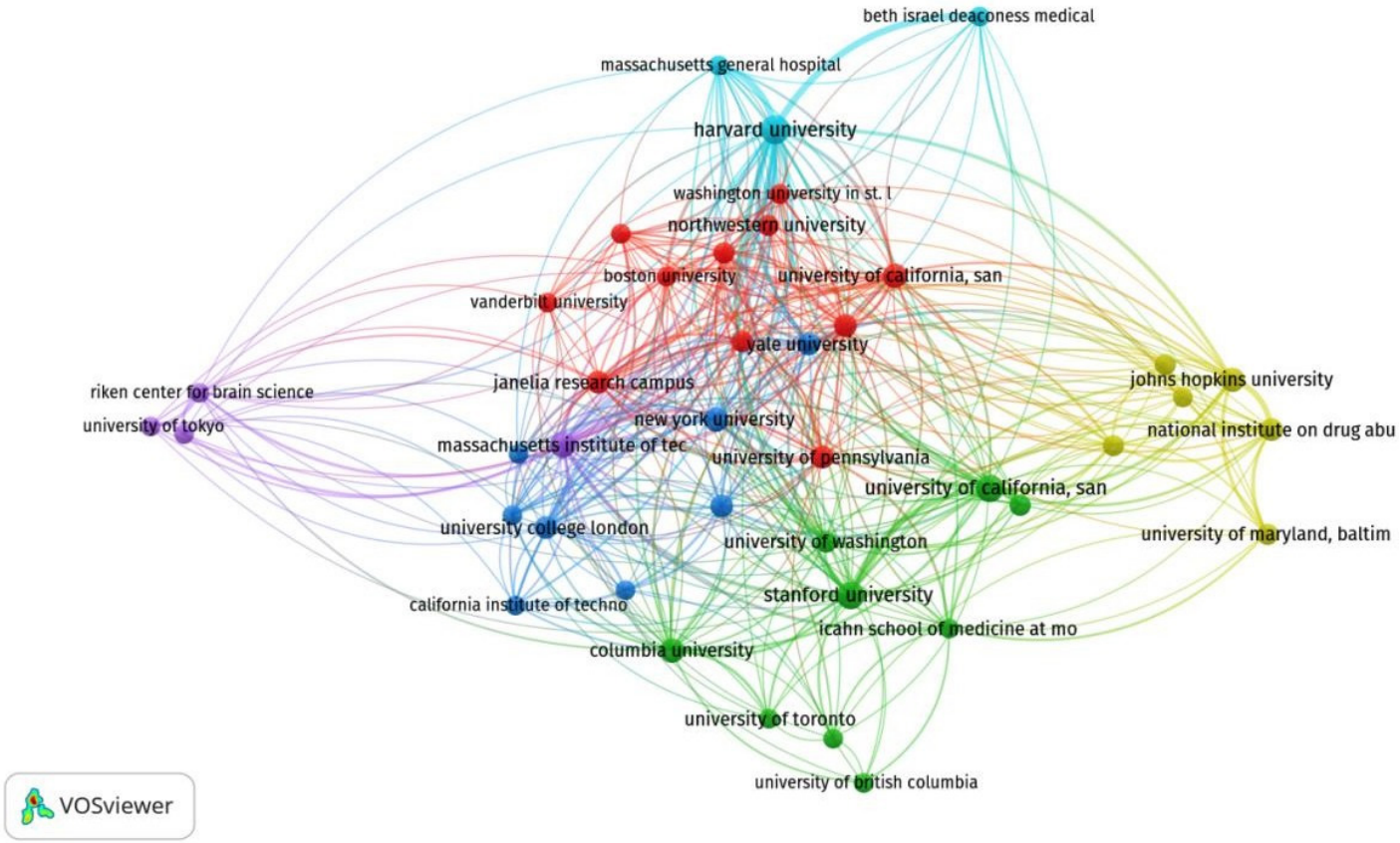


Figure 6: A map of institutional collaborations based on authors.

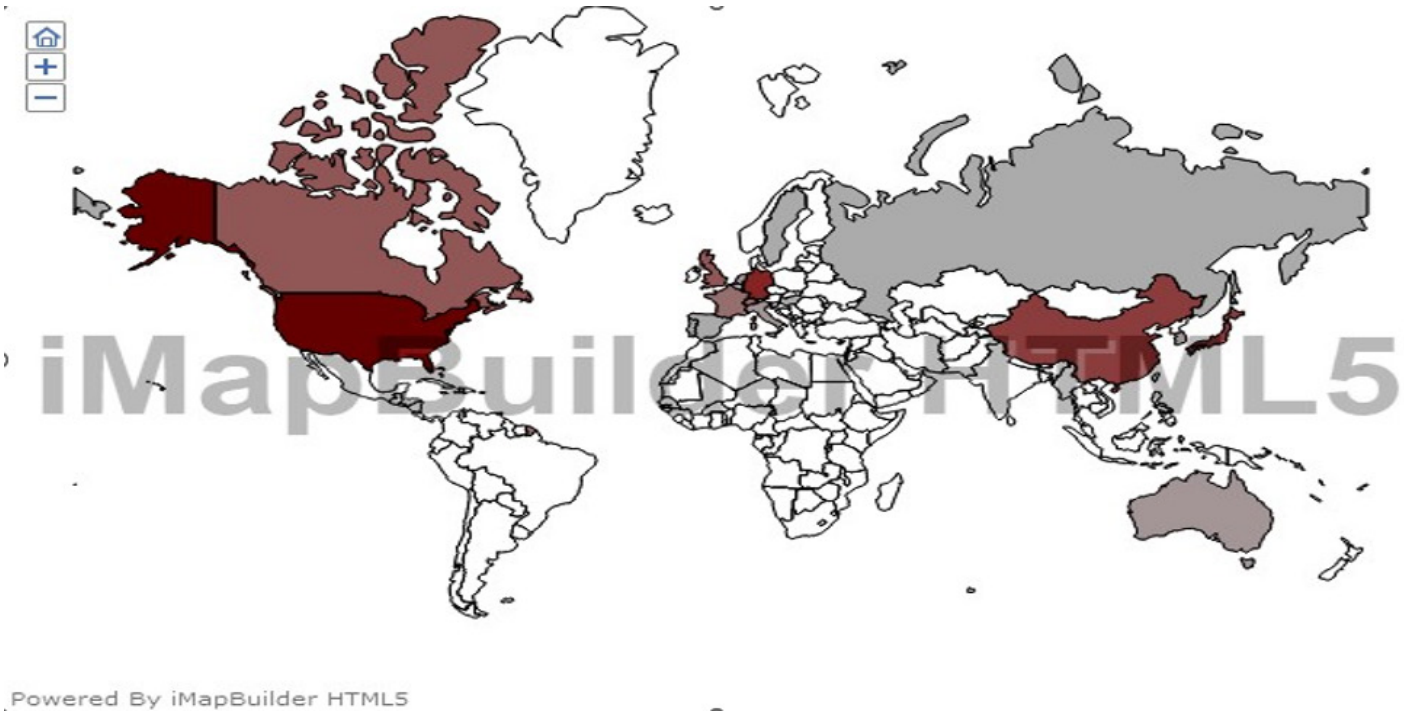


Figure 7: iMap Builder Heath Map based on the number of publications country wise.

Table 10: The most productive countries based on number of publications.

S1. No	Country	No. of Publications	Percentage of Publications (%)
1	United States	1715	46.5
2	Germany	249	6.8
3	Japan	195	5.3
4	China	193	5.2
5	United Kingdom	181	4.9
6	Canada	174	4.7
7	France	141	3.8
8	Switzerland	113	3.1

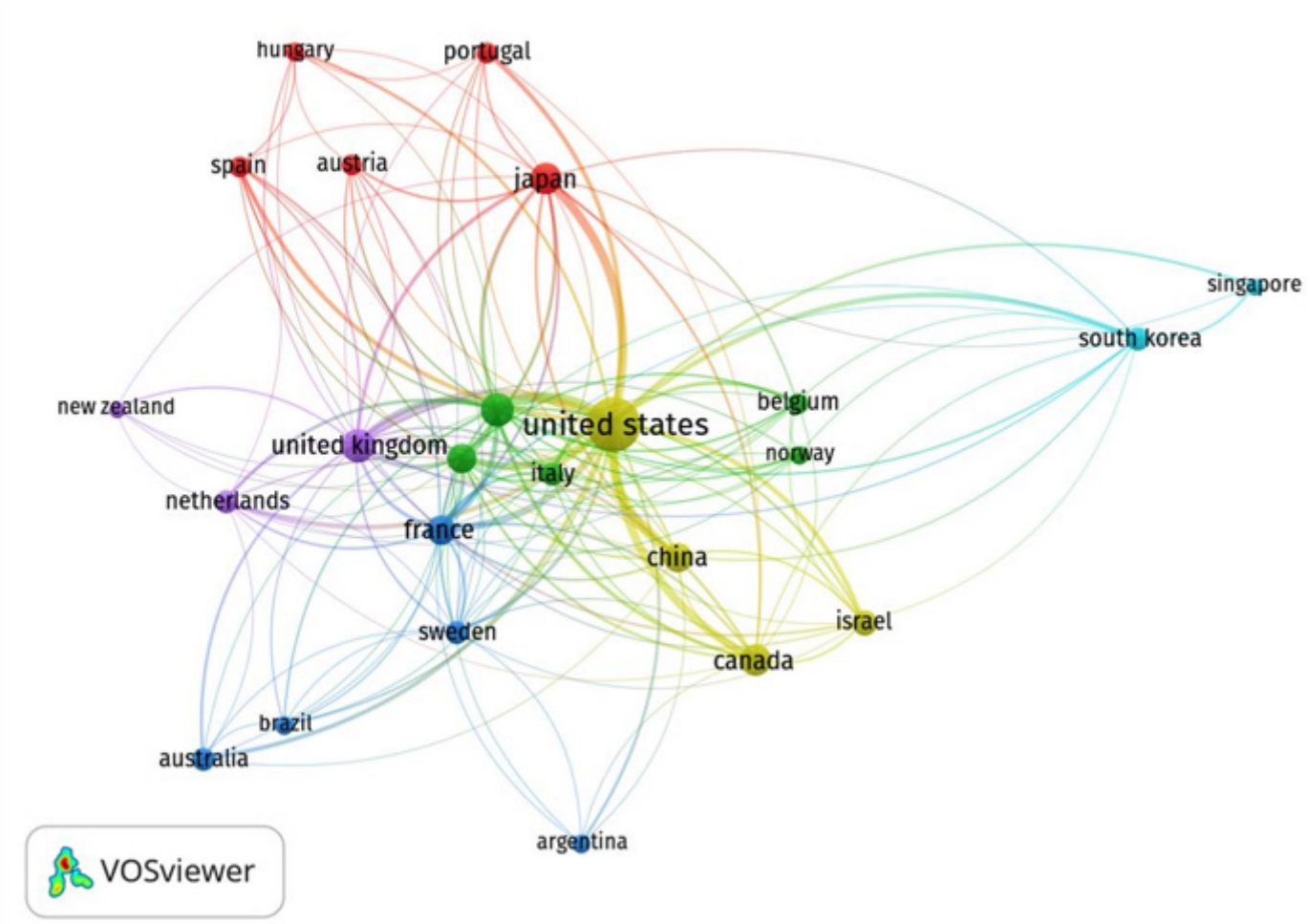


Figure 8: Network visualization map of international collaboration among countries with a minimum productivity of 10 documents (Minimum citations: 100).

and answering open-ended, difficult, and challenging questions. Thus, this lends credibility to the optogenetics technique, as it is used by well-renowned neuroscientists asking fundamental discovery-based questions related to Neuroscience and beyond.

In keeping with the high quality of neuroscientists, and of neuroscience using optogenetics as a technique, most of the publications using optogenetics were published in high impact neuroscience journals. Journals like Neuron, Nature Neuroscience, Journal of Neuroscience, Elife, and Frontiers in Neural Circuits. These journals have an Impact Factor (IF) greater than 5 suggesting high experimental rigor and stringent peer review of all included research documents. These journals publish original, novel, high-quality, authentic, cutting-edge, and supposedly

Table 11: The total number of document year wise (2010-2020).

Year	No of Documents	Percentage of Documents (%)
2010	21	15.7
2011	44	13.6
2012	91	14.6
2013	206	12.4
2014	211	10.9
2015	285	10.9
2016	286	8.1
2017	326	7.9
2018	382	3.5
2019	357	1.7
2020	412	0.8
Total	2621	100

reproducible experimental research in the neuroscience domain. Thus, the content in these journals is deemed to be trustworthy by the neuroscience community and therefore have widespread readership in the USA, and around the globe.

European (i.e., Germany, United Kingdom, France, Switzerland, and Italy) and a few Asian countries (i.e., Japan, China, South Korea, Australia) have also contributed substantially in terms of published documents and this could be related to the better collaborative ties between institutes/labs in the United States and these countries. Moreover collaborative grants between labs/investigators in these nations, and local funding sources in terms of grant agencies ensure the high productivity of high quality cutting edge research in Neuroscience. In keeping with this, the productivity of these countries is mirrored by the geographical positioning of grant agencies and bodies funding neuroscience applying optogenetics as a technique (i.e. National Institutes of Health, U.S. Department of Health and Human Services, National

Table 12: Average number of authors per document year wise (2010-2020).

Year	Frequency	% (*n*= 2621)	Total number of Authors	Authors per document (Average)
2010	21	0.8	86	4.1
2011	44	1.7	163	3.7
2012	91	3.5	376	4.1
2013	206	7.9	1040	5.0
2014	211	8.1	1030	4.9
2015	285	10.9	1612	5.7
2016	286	10.9	1549	5.4
2017	326	12.4	1914	5.9
2018	382	14.6	2733	7.2
2019	357	13.6	2190	6.1
2020	412	15.7	3244	7.9
Total	2621	100	15937	6.1

Table 13: Average Growth Rate (AGR), Relative Growth Rate (RGR), and Doubling Time (DT) of documents year wise (2010-2020).

Year	Frequency	AGR	% AGR	Cumulative total publications	loge W	RGR	DT
2010	21	----	----	21	3.0	----	----
2011	44	1.1	109.5	65	4.2	1.1	0.6
2012	91	1.1	106.8	156	5.0	0.9	0.8
2013	206	1.3	126.4	362	5.9	0.8	0.8
2014	211	0.0	2.4	573	6.4	0.5	1.5
2015	285	0.4	35.1	858	6.8	0.4	1.7
2016	286	0.0	0.4	1144	7.0	0.3	2.4
2017	326	0.1	14.0	1470	7.3	0.3	2.8
2018	382	0.2	17.2	1852	7.5	0.2	3.0
2019	357	-0.1	-6.5	2209	7.7	0.2	3.9
2020	412	0.2	15.4	2621	7.9	0.2	4.1

Table 14: Number of single-authored publications, number of multi-authored publications, Degree of Collaboration and Collaborative Index (CI).

Year	Frequency	% (*n*= 4546)	Total number of Authors	No of Single Author publications	% Of Single Authored publications	Number of Multi-Authored Publications	% Of Multi-authored publications	Number of authors in multi-Authored publications	Degree of collaboration	Collaborative Index (CI)
2010	21	0.5	86	6	28.6	15	71.4	80	0.7	5.3
2011	44	1.0	163	8	18.2	36	81.8	155	0.8	4.3
2012	91	2.0	376	10	11.0	81	89.0	366	0.9	4.5
2013	206	4.5	1040	10	4.9	196	95.1	1030	1.0	5.3
2014	211	4.6	1030	8	3.8	203	96.2	1022	1.0	5.0
2015	285	6.3	1612	9	3.2	276	96.8	1603	1.0	5.8
2016	286	6.3	1549	10	3.5	276	96.5	1539	1.0	5.6
2017	326	7.2	1914	8	2.5	318	97.5	1906	1.0	6.0
2018	382	8.4	2733	0	0.0	382	100.0	2733	1.0	7.2
2019	357	7.9	2190	14	3.9	343	96.1	2176	1.0	6.3
2020	412	9.1	3244	0	0.0	412	100.0	3244	1.0	7.9
Total	2621	100	15937	83	3.2	2538	96.8	15854	0.9	6.2

Institute of Neurological Disorders and Stroke, National Institute of Mental Health based in the USA; the European Commission, European Research Council, Deutsche Forschungsgemeinschaft in Europe; and the Japan Society for the Promotion of Science, National Natural Science Foundation of China in Asia).

Besides monetary considerations, installing an optogenetic setup and making sure it works appropriately requires substantial technological know-how and expertise in optics as well as electrophysiology. Firstly, an electrophysiological rig or implantable electrodes that have the capability of recording currents from cells/ populations of cells *in vivo, ex vivo*, or *in vitro*, is essential for labs that use optogenetics. Secondly, for *in vivo* studies, knowledge and capability of conducting stereotaxic surgeries to get the lentiviruses/adenoviruses carrying the opsin genes into the appropriate brain regions and requisite neurons is a must. Thirdly, using optogenetics *in vivo* for assessing circuitry casual or associated with certain behaviours/functions in real time requires implantation of the optic fiber into that particular region of the brain and making sure the optic fiber is stably placed while the animal is awake and behaving. Only under circumstances in which the optogenetics set-up is accurate, precise, and reliable, can this technique be used to answer neuroscience-based questions. Thus, financial resources and technical limitations could be some of the reasons hindering the application and usage of optogenetics in neuroscience labs within developing countries-some countries within the Asian sub-continent, Africa and South America. To bridge this gap, there is need for 1. More active collaborations between neuroscience labs that possess the optogenetics technique in the developed world and labs in developing countries, and 2. Labs that have the resources and technical expertise to pass on this knowledge to labs that wish to setup optogenetics in-house, especially neuroscience labs in developing countries. Writing collaborative grants between optogenetics-ready and optogenetics-devoid labs could be one such solution to reduce the financial burden, improve sharing of technical knowledge, and increasing the pace and quality of research in developing countries.

Literature using optogenetics in Neuroscience covered a wide range of areas from its applications in understanding underlying circuitry causative or associated with anxiety, depression, addiction, and motivation, to understanding local micro-circuit within, and long-range circuit connectivity between brain regions. Optogenetics gave neuroscientists the unique opportunity of identifying cellular pathways and circuitry involved in behaviours/behavioral actions due to its high spatial and temporal resolution. Due to optogenetics, the cellular (i.e., engrams) and the molecular underpinnings of learning and memory could be unraveled.[57,58] Answers to these questions eluded neuroscientists previously due to lack of an effective interrogative technique possessing high spatio-temporal resolution. The optogenetics technique has lead to a better understanding of connections and

circuitry within the brain necessary and/or sufficient for basic physiological functioning (hunger, thirst, circadian rhythms, sleep and awake states, etc.) as well as causative/underlying disease states (Parkinsons, Alzheimers, Amylotrophic Lateral Sclerosis, Fronto-Temporal Dementia, Stroke, Epilepsy, etc.).[59-64]

Despite such rapid pre-clinical progress using optogenetics over that past decade (i.e., studies in mice, rats and lower primates), the applicability of optogenetics on a large-scale level in humans remains as a question mark-particularly with regards to its applications in the CNS (i.e., brain).[65,66]

However, a few studies have shown the applicability of optogenetics in the human visual system, restoring sight in visually deficient people by transducing retinal ganglion cells with light sensitive opsins restoring vision.[67-69] Manipulating the activity of neurons in the human brain, spinal cord or peripheral nerves is currently not possible due to its invasiveness with respect to light delivery into the brain, and the lack of suitable methods to get opsins into the appropriate neurons or sets of neurons safely.[65,66] Even with the blossoming of non-invasive optogenetic techniques, optogenetics in humans has a long road ahead in terms of safety and efficacy testing.[70-72] Thus, with the possibility of unlimited therapeutic opportunities by applying optogenetics in humans, we all hope that optogenetics one day will have its time.

Even though optogenetics has no direct applications in human brains and brain circuits as of today, the data gleaned from pre-clinical studies are being used to inspire pharmacological as we'll as-pharmacological techniques. As a non-pharmacological technique, Deep Brain Stimulation (DBS) along with other neuromodulatory techniques are currently used to treat different neurological diseases such as parkinsons, epilepsy, essential tremor, dystonia and obsessive compulsive disorders.[73-77] Recent studies have hinted that neuromodulatory techniques, particularly DBS, can also be used as a potential treatment option for addictions, chronic pain, dementia, depression, traumatic brain injury, and neurodegenerative disorders such as Alzheimers, Huntington's disease, Multiple Sclerosis etc.[78-85] However, the underlying circuitry, pathways, cell types and connections giving rise to behaviours, and their association with disease states is still an area of active investigation-optogenetics playing a useful role in such investigations.[86,87] Knowledge gained from such preclinical studies could one day be used to target specific circuits in the human brain by DBS or other neuromodulatory techniques.[88] Thus, neuromodulatory techniques (i.e., DBS) inspired by optogenetics holds great promise for improving symptoms and in some cases reverting the course of disease of patients suffering from certain neurological disorders.[89-92] Thus, brain neuromodulatory techniques can be delivered to specific regions, cell types and/or axonal pathways to treat brain diseases with minimum possible side effects, unlike conventional drugs causing many unwanted side effects.

Besides informing brain neuromodulation, optogenetics holds therapeutic promise for pain relief and pleasure/hedonistic regulation (opto-morphs (MOPR), Kappa (KOPR), delta (DOPR), and Nociceptin Receptors (NOPR)), retinal sight restoration (Opto-mGluR6), and in optogenetic modulation of cell signaling-light sensitive cell surface receptors, transcription factors etc.[93-97] Optogenetic based gene editing techniques (Photo-activatable Cas9), and optogenetic enhanced regenerative capacity (light based cell regeneration techniques) applications have also shown immense therapeutic promise.[98-100]

Our study had a few limitations

First, the Scopus database includes only published literature and therefore this study could be biased towards published literature as opposed to grey literature, indexed journals, and language used in publications. Thus, there is a possibility of leaving out relevant studies that are not listed in the Scopus database. Second, due to the search query never being ideal in terms of formulation, false positives and false negatives can lead to non-relevant studies being included or removed. Thus, the total document count is to be expected with a certain margin of error; however, this should be small enough not to remain a significant factor. Third, it is important to keep in mind that the Scopus database is updated frequently with some journals periodically added or removed; this could therefore affect the current total count when the same search string is used. Third, the document count detected by Scopus could be lower than the actual count in instances when a single author or institution is represented by more than one name affecting the productivity of authors and institutions.

Besides these short comings, to our knowledge this is the first study to bibliometrically review neuroscience literature using optogenetics as a technique within the chosen study period.

CONCLUSION

Optogenetics has the potential to advance our understanding of the brain at circuit level detail in ways that were not possible before its discovery. Over the past 10 years (2010-2020); optogenetics, along with *in vivo* chemogenetics and muti-channel electrophysiology, have been cornerstone techniques in elucidating circuits and how they relate to behavior. This would not be possible without optogenetic's temporal and spatial precision. Credit to the authors that converted optogenetics from a nascent hard-to-use technique (between 2005-2010) to a highly applicable technique capable of solving a multitude of neuroscience based research questions and hypothesis (between 2010-2020). Furthermore, the future of optogenetics lays in how optogenetics can be adapted to cure and alleviate human disease burden, in particular brain diseases and mental disorders. Thus, we have reason to hope that optogenetics could switch gears with existing and upcoming non-invasive technologies to usher in a new era in neuroscience with a human therapy-centric focus.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Table 1: Author details (Name and Scopus ID), optogenetic related document count, year of 1st pubication, total publication count, *h*-index and total citations.

Ranking	Author name	Total document count	Year of 1st publication	Scopus Author ID	Total publication	*h*-index	Total citations
1	Deisseroth, K.	59	1990	6603640862	398	135	68179
2	Boyden, E.S.	26	2000	35291447700	208	67	19151
3	Yamanaka, A.	17	1997	55319368300	136	42	7084
4	Kravitz, A.V.	16	2004	6602759239	60	23	3403
5	Lee, J.H.	16	2002	57196135833	38	20	2194
6	Murphy, T.H.	15	1986	7401632487	175	59	12694
7	Nestler, E.J.	15	1977	7102006227	692	156	92273
8	Stuber, G.D.	15	2000	7007142142	105	48	10688
9	BuzsÃ¡ki, G.	14	1973	7006676856	390	132	70008
10	Kreitzer, A.C.	14	2000	6507247826	62	45	10304

Table 2: Top cited article by the most productive authors in the field of optogenetics.

Ranking	Author name	Most cited article in optogenetics	Times cited	Year	Journal
1	Deisseroth, K.	Optogenetics in Neural Systems	1185	2011	Neuron
2	Boyden, E.S.	A toolbox of Cre-dependent optogenetic transgenic mice for light-induced activation and silencing	690	2012	Nature Neuroscience
3	Yamanaka, A.	Acute optogenetic silencing of orexin/hypocretin neurons induces slow-wave sleep in mice	166	2011	Journal of Neuroscience
4	Kravitz, A.V.	Distinct roles for direct and indirect pathway striatal neurons in reinforcement	533	2012	Nature Neuroscience
5	Lee, J.H.	Frequency-selective control of cortical and subcortical networks by central thalamus	66	2015	eLife
6	Murphy, T.H.	Distinct Cortical Circuit Mechanisms for Complex Forelimb Movement and Motor Map Topography	92	2012	Neuron
7	Nestler, E.J.	The brain reward circuitry in mood disorders	865	2013	Nature Reviews Neuroscience
8	Stuber, G.D.	Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior	232	2011	Journal of Neuroscience
9	Buzsaki, G.	A toolbox of Cre-dependent optogenetic transgenic mice for light-induced activation and silencing	690	2012	Nature Neuroscience
10	Kreitzer, A.C.	Distinct roles for direct and indirect pathway striatal neurons in reinforcement	533	2012	Nature Neuroscience

Table 3: Top 10 journals with respect to Total Publications, Total Citations, Cite Score 2019, IF (Impact Factor), and *h*-index (2020).

Journal	Total Publications (TP) (2020)	Total Citations (TC) (2016-2019)	Cite Score 2019	IF (Impact Factor)	*h*-index (2020)
Journal of Neuroscience	3561	37553	10.5	5.6	14
Neuron	1448	36000	24.9	14.415	21
Nature Neuroscience	779	25093	32.2	20.0717	22
Elife	5574	60463	10.8	7.08	27
Frontiers in Neural Circuits	405	2373	5.9	3.156	5
Eneuro	1054	5211	4.9	3.544	7
Journal of Neurophysiology	1809	8132	4.5	2.225	6
Frontiers in Cellular Neuroscience	1705	9131	5.4	3.921	11
Current Opinion in Neurobiology	595	6422	10.8	6.528	11
Journal of Visualized Experiments	5213	9042	1.7	1.2	6

Table 4: Top 10 journals with respect to most cited articles and times-cited in 2020.

Journal	Most cited article (2020)	Times cited (2020)
Journal of Neuroscience	Microglia actively remodel adult hippocampal neurogenesis through the phagocytosis secretome.	51
Neuron	TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge.	64
Nature Neuroscience	Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain.	85
Elife	SARS-CoV-2 (COVID-19) by the numbers.	149
Frontiers in Neural Circuits	Multiplex Neural Circuit Tracing With G-Deleted Rabies Viral Vectors.	10
Eneuro	High-fat diet-induced obesity causes sex-specific deficits in adult hippocampal neurogenesis in mice.	13
Journal of Neurophysiology	Parallel distributed networks dissociate episodic and social functions within the individual.	22
Frontiers in Cellular Neuroscience	Cellular Senescence in Neurodegenerative Diseases.	30
Current Opinion in Neurobiology	Deep learning tools for the measurement of animal behavior in neuroscience.	31
Journal of Visualized Experiments	Measurement of the hepatic venous pressure gradient and transjugular liver biopsy.	10