US012383741B2

(12) United States Patent
Levine et al.

(10) **Patent No.: US 12,383,741 B2**
(45) **Date of Patent: *Aug. 12, 2025**

(54) **SYSTEMS AND METHODS FOR STIMULATING AND/OR MONITORING LOCI IN THE BRAIN TO TREAT INFLAMMATION AND TO ENHANCE VAGUS NERVE STIMULATION**

(71) Applicant: **SetPoint Medical Corporation**, Valencia, CA (US)

(72) Inventors: **Jacob A. Levine**, West Hempstead, NY (US); **Michael A. Faltys**, Valencia, CA (US)

(73) Assignee: **SetPoint Medical Corporation**, Valencia, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1 day.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/728,765**

(22) Filed: **Apr. 25, 2022**

(65) **Prior Publication Data**

US 2022/0257941 A1 Aug. 18, 2022

Related U.S. Application Data

(62) Division of application No. 14/922,022, filed on Oct. 23, 2015, now Pat. No. 11,311,725.

(Continued)

(51) **Int. Cl.**

A61N 1/36 (2006.01)
A61B 5/00 (2006.01)

(Continued)

(52) **U.S. Cl.**

CPC *A61N 1/3606* (2013.01); *A61B 5/369* (2021.01); *A61N 1/0526* (2013.01);

(Continued)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,164,121	A	6/1939	Pescador
3,363,623	A	1/1968	Atwell

(Continued)

FOREIGN PATENT DOCUMENTS

CN	201230913	A	5/2009
CN	101528303	A	9/2009

(Continued)

OTHER PUBLICATIONS

US 6,184,239 B1, 02/2001, Puskas (withdrawn)

(Continued)

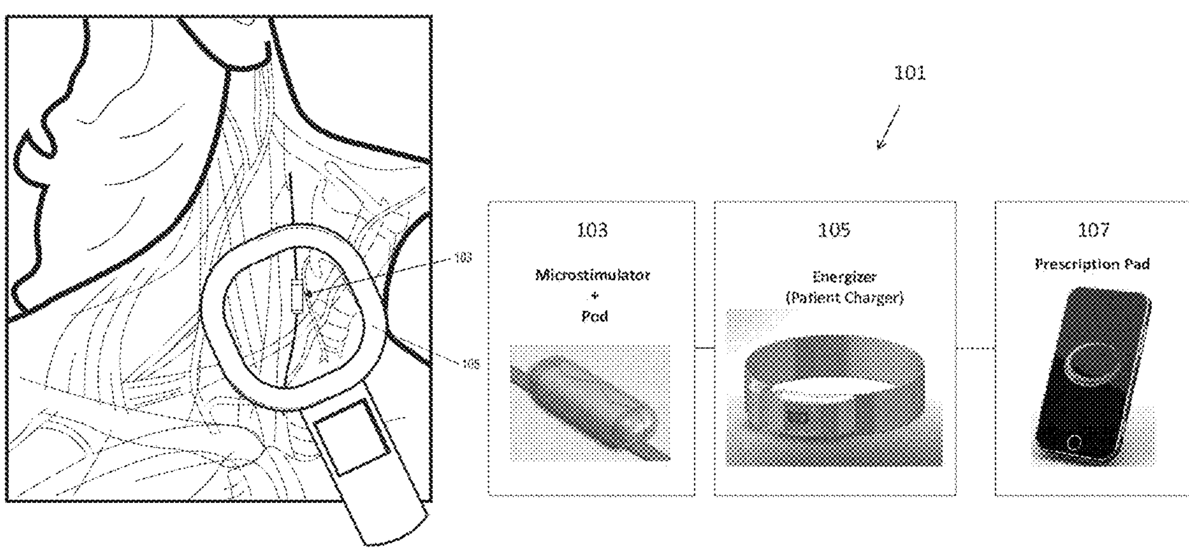
Primary Examiner — Jay B Shah

(74) *Attorney, Agent, or Firm* — Shay Glenn LLP

(57) **ABSTRACT**

Described herein are methods and systems for using EEG recordings to improve vagus nerve stimulation (VNS) therapy. In particular, described herein are methods and systems for using EEG recordings to detect P300 and/or activation of the nucleus basalis and/or the locus coeruleus to determine the efficacy of VNS. The EEG recordings can be used to provide feedback control to help optimize stimulation parameters and to screen for patients that respond well to VNS therapy.

20 Claims, 16 Drawing Sheets



Related U.S. Application Data

(60) Provisional application No. 62/068,473, filed on Oct. 24, 2014.

(51) **Int. Cl.**

A61B 5/369	(2021.01)
A61B 5/377	(2021.01)
A61N 1/05	(2006.01)
A61N 1/372	(2006.01)
A61N 1/375	(2006.01)
A61N 1/378	(2006.01)
A61N 2/00	(2006.01)
A61N 2/02	(2006.01)

(52) **U.S. Cl.**

CPC ***A61N 1/0529*** (2013.01); ***A61N 1/0551*** (2013.01); ***A61N 1/36053*** (2013.01); ***A61N 1/36125*** (2013.01); ***A61N 1/36135*** (2013.01); ***A61N 1/36139*** (2013.01); ***A61N 1/36146*** (2013.01); ***A61N 1/37205*** (2013.01); ***A61N 1/3756*** (2013.01); ***A61N 2/006*** (2013.01); *A61B 5/377* (2021.01); *A61B 5/4041* (2013.01); *A61B 5/4064* (2013.01); *A61N 1/0534* (2013.01); *A61N 1/0556* (2013.01); *A61N 1/37247* (2013.01); *A61N 1/3758* (2013.01); *A61N 1/3787* (2013.01); *A61N 2/02* (2013.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,631,534	A	12/1971	Hirota et al.
4,073,296	A	2/1978	McCall
4,098,277	A	7/1978	Mendell
4,305,402	A	12/1981	Katims
4,503,863	A	3/1985	Katims
4,573,481	A	3/1986	Bullara
4,590,946	A	5/1986	Loeb
4,632,095	A	12/1986	Libin
4,649,936	A	3/1987	Ungar et al.
4,702,254	A	10/1987	Zabara
4,840,793	A	6/1989	Todd, III et al.
4,867,164	A	9/1989	Zabara
4,929,734	A	5/1990	Coughenour et al.
4,930,516	A	6/1990	Alfano et al.
4,935,234	A	6/1990	Todd, III et al.
4,979,511	A	12/1990	Terry, Jr.
4,991,578	A	2/1991	Cohen
5,019,648	A	5/1991	Schlossman et al.
5,025,807	A	6/1991	Zabara
5,038,781	A	8/1991	Lynch
5,049,659	A	9/1991	Cantor et al.
5,073,560	A	12/1991	Wu et al.
5,106,853	A	4/1992	Showell et al.
5,111,815	A	5/1992	Mower
5,154,172	A	10/1992	Terry, Jr. et al.
5,175,166	A	12/1992	Dunbar et al.
5,179,950	A	1/1993	Stanislaw
5,186,170	A	2/1993	Varrichio et al.
5,188,104	A	2/1993	Wernicke et al.
5,203,326	A	4/1993	Collins
5,205,285	A	4/1993	Baker, Jr.
5,215,086	A	6/1993	Terry, Jr. et al.
5,215,089	A	6/1993	Baker, Jr.
5,222,494	A	6/1993	Baker, Jr.
5,231,988	A	8/1993	Wernicke et al.
5,235,980	A	8/1993	Varrichio et al.
5,237,991	A	8/1993	Baker et al.
5,251,634	A	10/1993	Weinberg
5,263,480	A	11/1993	Wernicke et al.
5,269,303	A	12/1993	Wernicke et al.
5,299,569	A	4/1994	Wernicke et al.
5,304,206	A	4/1994	Baker, Jr. et al.
5,330,507	A	7/1994	Schwartz
5,330,515	A	7/1994	Rutecki et al.
5,335,657	A	8/1994	Terry, Jr. et al.
5,344,438	A	9/1994	Testerman et al.
5,351,394	A	10/1994	Weinberg
5,403,845	A	4/1995	Dunbar et al.
5,458,625	A	10/1995	Kendall
5,472,841	A	12/1995	Jayasena et al.
5,487,756	A	1/1996	Kallesoe et al.
5,496,938	A	3/1996	Gold et al.
5,503,978	A	4/1996	Schneider et al.
5,531,778	A	7/1996	Maschino et al.
5,540,730	A	7/1996	Terry, Jr. et al.
5,540,734	A	7/1996	Zabara
5,567,588	A	10/1996	Gold et al.
5,567,724	A	10/1996	Kelleher et al.
5,571,150	A	11/1996	Wernicke et al.
5,580,737	A	12/1996	Polisky et al.
5,582,981	A	12/1996	Toole et al.
5,604,231	A	2/1997	Smith et al.
5,607,459	A	3/1997	Paul et al.
5,611,350	A	3/1997	John
5,618,818	A	4/1997	Ojo et al.
5,629,285	A	5/1997	Black et al.
5,637,459	A	6/1997	Burke et al.
5,651,378	A	7/1997	Matheny et al.
5,654,151	A	8/1997	Allen et al.
5,683,867	A	11/1997	Biesecker et al.
5,690,681	A	11/1997	Geddes et al.
5,690,693	A	11/1997	Wang et al.
5,700,282	A	12/1997	Zabara
5,705,337	A	1/1998	Gold et al.
5,707,400	A	1/1998	Terry, Jr. et al.
5,709,853	A	1/1998	Lino et al.
5,712,375	A	1/1998	Jensen et al.
5,718,912	A	2/1998	Thompson et al.
5,726,017	A	3/1998	Lochrie et al.
5,726,179	A	3/1998	Messer, Jr. et al.
5,727,556	A	3/1998	Weth et al.
5,733,255	A	3/1998	Dinh et al.
5,741,802	A	4/1998	Kem et al.
5,773,598	A	6/1998	Burke et al.
5,786,462	A	7/1998	Schneider et al.
5,788,656	A	8/1998	Mino
5,792,210	A	8/1998	Wamubu et al.
5,824,027	A	10/1998	Hoffer et al.
5,853,005	A	12/1998	Scanlon
5,854,289	A	12/1998	Bianchi et al.
5,902,814	A	5/1999	Gordon et al.
5,913,876	A	6/1999	Taylor et al.
5,916,239	A	6/1999	Geddes et al.
5,919,216	A	7/1999	Houben et al.
5,928,272	A	7/1999	Adkins et al.
5,964,794	A	10/1999	Bolz et al.
5,977,144	A	11/1999	Meyer et al.
5,994,330	A	11/1999	El Khoury
6,002,964	A	12/1999	Feler et al.
6,006,134	A	12/1999	Hill et al.
6,017,891	A	1/2000	Eibl et al.
6,028,186	A	2/2000	Tasset et al.
6,051,017	A	4/2000	Loeb et al.
6,083,696	A	7/2000	Biesecker et al.
6,083,905	A	7/2000	Voorberg et al.
6,096,728	A	8/2000	Collins et al.
6,104,956	A	8/2000	Naritoku et al.
6,110,900	A	8/2000	Gold et al.
6,110,914	A	8/2000	Phillips et al.
6,117,837	A	9/2000	Tracey et al.
6,124,449	A	9/2000	Gold et al.
6,127,119	A	10/2000	Stephens et al.
6,140,490	A	10/2000	Biesecker et al.
6,141,590	A	10/2000	Renirie et al.
6,147,204	A	11/2000	Gold et al.
6,159,145	A	12/2000	Satoh
6,164,284	A	12/2000	Schulman et al.
6,166,048	A	12/2000	Bencherif
6,168,778	B1	1/2001	Janjic et al.
6,171,795	B1	1/2001	Korman et al.
6,205,359	B1	3/2001	Boveja

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,208,894 B1	3/2001	Schulman et al.	
6,208,902 B1	3/2001	Boveja	
6,210,321 B1	4/2001	Di Mino et al.	
6,224,862 B1	5/2001	Turecek et al.	
6,233,488 B1	5/2001	Hess	
6,266,564 B1	7/2001	Hill et al.	
6,269,270 B1	7/2001	Boveja	
6,304,775 B1	10/2001	Iasemidis et al.	
6,308,104 B1	10/2001	Taylor et al.	
6,337,997 B1	1/2002	Rise	
6,339,725 B1	1/2002	Naritoku et al.	
6,341,236 B1	1/2002	Osorio et al.	
6,356,787 B1	3/2002	Rezai et al.	
6,356,788 B2	3/2002	Boveja	
6,381,499 B1	4/2002	Taylor et al.	
6,405,732 B1	6/2002	Edwards et al.	
6,407,095 B1	6/2002	Lochead et al.	
6,428,484 B1	8/2002	Battmer et al.	
6,429,217 B1	8/2002	Puskas	
6,447,443 B1	9/2002	Keogh et al.	
6,449,507 B1	9/2002	Hill et al.	
6,473,644 B1	10/2002	Terry, Jr. et al.	
6,479,523 B1	11/2002	Puskas	
6,487,446 B1	11/2002	Hill et al.	
6,511,500 B1	1/2003	Rahme	
6,528,529 B1	3/2003	Brann et al.	
6,532,388 B1	3/2003	Hill et al.	
6,542,774 B2	4/2003	Hill et al.	
6,556,868 B2	4/2003	Naritoku et al.	
6,564,102 B1	5/2003	Boveja	
6,587,719 B1	7/2003	Barrett et al.	
6,587,727 B2	7/2003	Osorio et al.	
6,600,956 B2	7/2003	Maschino et al.	
6,602,891 B2	8/2003	Messer et al.	
6,609,025 B2	8/2003	Barrett et al.	
6,610,713 B2	8/2003	Tracey	
6,611,715 B1	8/2003	Boveja	
6,615,081 B1	9/2003	Boveja	
6,615,085 B1	9/2003	Boveja	
6,622,038 B2	9/2003	Barrett et al.	
6,622,041 B2	9/2003	Terry, Jr. et al.	
6,622,047 B2	9/2003	Barrett et al.	
6,628,987 B1	9/2003	Hill et al.	
6,633,779 B1	10/2003	Schuler et al.	
6,656,960 B2	12/2003	Puskas	
6,668,191 B1	12/2003	Boveja	
6,671,556 B2	12/2003	Osorio et al.	
6,684,105 B2	1/2004	Cohen et al.	
6,690,973 B2	2/2004	Hill et al.	
6,718,208 B2	4/2004	Hill et al.	
6,721,603 B2	4/2004	Zabara et al.	
6,735,471 B2	5/2004	Hill et al.	
6,735,474 B1	5/2004	Loeb et al.	
6,735,475 B1	5/2004	Whitehurst et al.	
6,760,626 B1	7/2004	Boveja	
6,762,032 B1	7/2004	Nelson et al.	
6,778,854 B2	8/2004	Puskas	
6,804,558 B2	10/2004	Haller et al.	
RE38,654 E	11/2004	Hill et al.	
6,826,428 B1	11/2004	Chen et al.	
6,832,114 B1	12/2004	Whitehurst et al.	
6,838,471 B2	1/2005	Tracey	
RE38,705 E	2/2005	Hill et al.	
6,879,859 B1	4/2005	Boveja	
6,885,888 B2	4/2005	Rezai	
6,901,294 B1	5/2005	Whitehurst et al.	
6,904,318 B2	6/2005	Hill et al.	
6,920,357 B2	7/2005	Osorio et al.	
6,928,320 B2	8/2005	King	
6,934,583 B2	8/2005	Weinberg et al.	
6,937,903 B2	8/2005	Schuler et al.	
6,961,618 B2	11/2005	Osorio et al.	
6,978,787 B1	12/2005	Broniatowski	
7,011,638 B2	3/2006	Schuler et al.	
7,054,686 B2	5/2006	MacDonald	
7,054,692 B1	5/2006	Whitehurst et al.	
7,058,447 B2	6/2006	Hill et al.	
7,062,320 B2	6/2006	Ehlinger, Jr.	
7,069,082 B2	6/2006	Lindenthaler	
7,072,720 B2	7/2006	Puskas	
7,076,307 B2	7/2006	Boveja et al.	
7,142,910 B2	11/2006	Puskas	
7,142,917 B2	11/2006	Fukui	
7,149,574 B2	12/2006	Yun et al.	
7,155,279 B2	12/2006	Whitehurst et al.	
7,155,284 B1	12/2006	Whitehurst et al.	
7,167,750 B2	1/2007	Knudson et al.	
7,167,751 B1	1/2007	Whitehurst et al.	
7,174,218 B1	2/2007	Kuzma	
7,184,828 B2	2/2007	Hill et al.	
7,184,829 B2	2/2007	Hill et al.	
7,191,012 B2	3/2007	Boveja et al.	
7,204,815 B2	4/2007	Connor	
7,209,787 B2	4/2007	DiLorenzo	
7,225,019 B2	5/2007	Jahns et al.	
7,228,167 B2	6/2007	Kara et al.	
7,238,715 B2	7/2007	Tracey et al.	
7,242,984 B2	7/2007	DiLorenzo	
7,269,457 B2	9/2007	Shafer et al.	
7,345,178 B2	3/2008	Nunes et al.	
7,373,204 B2	5/2008	Gelfand et al.	
7,389,145 B2	6/2008	Kilgore et al.	
7,454,245 B2	11/2008	Armstrong et al.	
7,467,016 B2	12/2008	Colborn	
7,499,752 B2 *	3/2009	Maschino	A61N 1/36082 607/40
7,544,497 B2	6/2009	Sinclair et al.	
7,561,918 B2	7/2009	Armstrong et al.	
7,634,315 B2	12/2009	Cholette	
7,711,432 B2	5/2010	Thimineur et al.	
7,729,760 B2	6/2010	Patel et al.	
7,751,891 B2	7/2010	Armstrong et al.	
7,776,326 B2	8/2010	Milbrandt et al.	
7,797,058 B2	9/2010	Mrva et al.	
7,819,883 B2	10/2010	Westlund et al.	
7,822,486 B2	10/2010	Foster et al.	
7,829,556 B2	11/2010	Bemis et al.	
7,869,869 B1	1/2011	Farazi	
7,869,885 B2	1/2011	Begnaud et al.	
7,937,145 B2	5/2011	Dobak	
7,962,220 B2	6/2011	Kolafa et al.	
7,974,701 B2	7/2011	Armstrong	
7,974,707 B2	7/2011	Inman	
7,996,088 B2	8/2011	Marrosu et al.	
7,996,092 B2	8/2011	Mrva et al.	
8,019,419 B1	9/2011	Panescu et al.	
8,060,208 B2	11/2011	Kilgore et al.	
8,103,349 B2	1/2012	Donders et al.	
8,165,668 B2	4/2012	Dacey, Jr. et al.	
8,180,446 B2	5/2012	Dacey, Jr. et al.	
8,180,447 B2	5/2012	Dacey et al.	
8,195,287 B2	6/2012	Dacey, Jr. et al.	
8,214,056 B2	7/2012	Hoffer et al.	
8,233,982 B2	7/2012	Libbus	
8,391,970 B2	3/2013	Tracey et al.	
8,412,338 B2	4/2013	Faltys	
8,504,161 B1	8/2013	Kornet et al.	
8,571,654 B2	10/2013	Libbus et al.	
8,577,458 B1	11/2013	Libbus et al.	
8,600,505 B2	12/2013	Libbus et al.	
8,612,002 B2	12/2013	Faltys et al.	
8,630,709 B2	1/2014	Libbus et al.	
8,688,212 B2	4/2014	Libbus et al.	
8,700,150 B2	4/2014	Libbus et al.	
8,729,129 B2	5/2014	Tracey et al.	
8,788,034 B2	7/2014	Levine et al.	
8,843,210 B2	9/2014	Simon et al.	
8,855,767 B2	10/2014	Faltys et al.	
8,886,339 B2	11/2014	Faltys et al.	
8,914,114 B2	12/2014	Tracey et al.	
8,918,178 B2	12/2014	Simon et al.	
8,918,191 B2	12/2014	Libbus et al.	
8,923,964 B2	12/2014	Libbus et al.	
8,983,628 B2	3/2015	Simon et al.	

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,983,629	B2	3/2015	Simon et al.
8,996,116	B2	3/2015	Faltys et al.
9,114,262	B2	8/2015	Libbus et al.
9,162,064	B2	10/2015	Faltys et al.
9,174,041	B2	11/2015	Faltys et al.
9,211,409	B2	12/2015	Tracey et al.
9,211,410	B2	12/2015	Levine et al.
9,254,383	B2	2/2016	Simon et al.
9,272,143	B2	3/2016	Libbus et al.
9,358,381	B2	6/2016	Simon et al.
9,399,134	B2	7/2016	Simon et al.
9,403,001	B2	8/2016	Simon et al.
9,409,024	B2	8/2016	KenKnight et al.
9,415,224	B2	8/2016	Libbus et al.
9,452,290	B2	9/2016	Libbus et al.
9,504,832	B2	11/2016	Libbus et al.
9,511,228	B2	12/2016	Amurthur et al.
9,533,153	B2	1/2017	Libbus et al.
9,572,983	B2	2/2017	Levine et al.
9,662,490	B2	5/2017	Tracey et al.
9,700,716	B2	7/2017	Faltys et al.
9,833,621	B2	12/2017	Levine
9,849,286	B2	12/2017	Levine et al.
9,987,492	B2	6/2018	Tracey et al.
9,993,651	B2	6/2018	Faltys et al.
10,166,395	B2	1/2019	Tracey et al.
10,220,203	B2	3/2019	Faltys et al.
10,449,358	B2	10/2019	Levine et al.
10,561,846	B2	2/2020	Tracey et al.
10,583,304	B2	3/2020	Faltys et al.
10,596,367	B2	3/2020	Faltys et al.
10,695,569	B2	6/2020	Levine et al.
10,716,936	B2	7/2020	Faltys et al.
10,912,712	B2	2/2021	Tracey et al.
11,051,744	B2	7/2021	Levine et al.
11,110,287	B2	9/2021	Faltys et al.
11,173,307	B2	11/2021	Levine et al.
11,207,518	B2	12/2021	Huston et al.
11,260,229	B2	3/2022	Manogue
11,278,718	B2	3/2022	Faltys et al.
11,311,725	B2	4/2022	Levine et al.
11,344,724	B2	5/2022	Huston et al.
11,383,091	B2	7/2022	Faltys et al.
2001/0002441	A1	5/2001	Boveja
2001/0034542	A1	10/2001	Mann
2002/0026141	A1	2/2002	Houben et al.
2002/0040035	A1	4/2002	Myers et al.
2002/0077675	A1	6/2002	Greenstein
2002/0086871	A1	7/2002	O'Neill et al.
2002/0095139	A1	7/2002	Keogh et al.
2002/0099417	A1	7/2002	Naritoku et al.
2002/0138075	A1	9/2002	Edwards et al.
2002/0138109	A1	9/2002	Keogh et al.
2002/0193859	A1	12/2002	Schulman et al.
2002/0198570	A1	12/2002	Puskas
2003/0018367	A1	1/2003	DiLorenzo
2003/0032852	A1	2/2003	Perreault et al.
2003/0045909	A1	3/2003	Gross et al.
2003/0088301	A1	5/2003	King
2003/0191404	A1	10/2003	Klein
2003/0194752	A1	10/2003	Anderson et al.
2003/0195578	A1	10/2003	Perron et al.
2003/0212440	A1	11/2003	Boveja
2003/0229380	A1	12/2003	Adams et al.
2003/0236557	A1	12/2003	Whitehurst et al.
2003/0236558	A1	12/2003	Whitehurst et al.
2004/0002546	A1	1/2004	Altschuler
2004/0015202	A1	1/2004	Chandler et al.
2004/0015204	A1	1/2004	Whitehurst et al.
2004/0015205	A1	1/2004	Whitehurst et al.
2004/0024422	A1	2/2004	Hill et al.
2004/0024428	A1	2/2004	Barrett et al.
2004/0024439	A1	2/2004	Riso
2004/0030362	A1	2/2004	Hill et al.
2004/0039427	A1	2/2004	Barrett et al.
2004/0048795	A1	3/2004	Ivanova et al.
2004/0049121	A1	3/2004	Yaron
2004/0049240	A1	3/2004	Gerber et al.
2004/0059383	A1	3/2004	Puskas
2004/0111139	A1	6/2004	McCreery et al.
2004/0138517	A1	7/2004	Osorio et al.
2004/0138518	A1	7/2004	Rise et al.
2004/0138536	A1	7/2004	Frei et al.
2004/0146949	A1	7/2004	Tan et al.
2004/0153127	A1	8/2004	Gordon et al.
2004/0158119	A1	8/2004	Osorio et al.
2004/0162584	A1	8/2004	Hill et al.
2004/0172074	A1	9/2004	Yoshihito
2004/0172085	A1	9/2004	Knudson et al.
2004/0172086	A1	9/2004	Knudson et al.
2004/0172088	A1	9/2004	Knudson et al.
2004/0172094	A1	9/2004	Cohen et al.
2004/0176812	A1	9/2004	Knudson et al.
2004/0178706	A1	9/2004	D'Orso
2004/0193231	A1	9/2004	David et al.
2004/0199209	A1	10/2004	Hill et al.
2004/0199210	A1	10/2004	Shelchuk
2004/0204355	A1	10/2004	Tracey et al.
2004/0215272	A1	10/2004	Haubrich et al.
2004/0215287	A1	10/2004	Swoyer et al.
2004/0236381	A1	11/2004	Dinsmoor et al.
2004/0236382	A1	11/2004	Dinsmoor et al.
2004/0240691	A1	12/2004	Grafenberg
2004/0243182	A1	12/2004	Cohen et al.
2004/0243211	A1	12/2004	Colliou et al.
2004/0254612	A1	12/2004	Ezra et al.
2004/0267152	A1	12/2004	Pineda
2005/0021092	A1	1/2005	Yun et al.
2005/0021101	A1	1/2005	Chen et al.
2005/0027328	A1	2/2005	Greenstein
2005/0043774	A1	2/2005	Devlin et al.
2005/0049655	A1	3/2005	Boveja et al.
2005/0065553	A1	3/2005	Ben Ezra et al.
2005/0065573	A1	3/2005	Rezai
2005/0065575	A1	3/2005	Dobak
2005/0070970	A1	3/2005	Knudson et al.
2005/0070974	A1	3/2005	Knudson et al.
2005/0075694	A1	4/2005	Schmeling et al.
2005/0075698	A1	4/2005	Phillips et al.
2005/0075701	A1	4/2005	Shafer
2005/0075702	A1	4/2005	Shafer
2005/0095246	A1	5/2005	Shafer
2005/0096707	A1	5/2005	Hill et al.
2005/0103351	A1	5/2005	Stomberg et al.
2005/0113894	A1	5/2005	Zilberman et al.
2005/0131467	A1	6/2005	Boveja
2005/0131486	A1	6/2005	Boveja et al.
2005/0131487	A1	6/2005	Boveja
2005/0131493	A1	6/2005	Boveja et al.
2005/0137644	A1	6/2005	Boveja et al.
2005/0137645	A1	6/2005	Voipio et al.
2005/0143781	A1	6/2005	Carbunaru et al.
2005/0143787	A1	6/2005	Boveja et al.
2005/0149126	A1	7/2005	Libbus
2005/0149129	A1	7/2005	Libbus et al.
2005/0149131	A1	7/2005	Libbus et al.
2005/0153885	A1	7/2005	Yun et al.
2005/0154425	A1	7/2005	Boveja et al.
2005/0154426	A1	7/2005	Boveja et al.
2005/0165458	A1	7/2005	Boveja et al.
2005/0177200	A1	8/2005	George et al.
2005/0182288	A1	8/2005	Zabara
2005/0182467	A1	8/2005	Hunter et al.
2005/0187584	A1	8/2005	Denker et al.
2005/0187586	A1	8/2005	David et al.
2005/0187590	A1	8/2005	Boveja et al.
2005/0191661	A1	9/2005	Gatanaga et al.
2005/0192644	A1	9/2005	Boveja et al.
2005/0197600	A1	9/2005	Schuler et al.
2005/0197675	A1	9/2005	David et al.
2005/0197678	A1	9/2005	Boveja et al.
2005/0203501	A1	9/2005	Aldrich et al.
2005/0209654	A1	9/2005	Boveja et al.
2005/0216064	A1	9/2005	Heruth et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2005/0216070	A1	9/2005	Boveja et al.
2005/0216071	A1	9/2005	Devlin et al.
2005/0240229	A1	10/2005	Whitehurst et al.
2005/0240231	A1	10/2005	Aldrich et al.
2005/0240241	A1	10/2005	Yun et al.
2005/0240242	A1	10/2005	DiLorenzo
2005/0251220	A1	11/2005	Barrett et al.
2005/0251222	A1	11/2005	Barrett et al.
2005/0267542	A1	12/2005	David et al.
2005/0267547	A1	12/2005	Knudson et al.
2005/0277912	A1	12/2005	John
2005/0283198	A1	12/2005	Haubrich et al.
2006/0009815	A1	1/2006	Boveja et al.
2006/0015151	A1	1/2006	Aldrich
2006/0025828	A1	2/2006	Armstrong et al.
2006/0036293	A1	2/2006	Whitehurst et al.
2006/0052657	A9	3/2006	Zabara
2006/0052831	A1	3/2006	Fukui
2006/0052836	A1	3/2006	Kim et al.
2006/0058851	A1	3/2006	Cigaina
2006/0064137	A1	3/2006	Stone
2006/0064139	A1	3/2006	Chung et al.
2006/0074450	A1	4/2006	Boveja et al.
2006/0074473	A1	4/2006	Gertner
2006/0079936	A1	4/2006	Boveja et al.
2006/0085046	A1	4/2006	Rezai et al.
2006/0095081	A1	5/2006	Zhou et al.
2006/0095090	A1	5/2006	De Ridder
2006/0100668	A1	5/2006	Ben-David et al.
2006/0106755	A1	5/2006	Stuhec
2006/0111644	A1	5/2006	Guttag et al.
2006/0111754	A1	5/2006	Rezai et al.
2006/0111755	A1	5/2006	Stone et al.
2006/0116739	A1	6/2006	Betser et al.
2006/0122675	A1	6/2006	Libbus et al.
2006/0129200	A1	6/2006	Kurokawa
2006/0129202	A1	6/2006	Armstrong
2006/0135998	A1	6/2006	Libbus et al.
2006/0136024	A1	6/2006	Cohen et al.
2006/0142802	A1	6/2006	Armstrong
2006/0142822	A1	6/2006	Tulgar
2006/0149337	A1	7/2006	John
2006/0155495	A1	7/2006	Osorio et al.
2006/0161216	A1	7/2006	John et al.
2006/0161217	A1	7/2006	Jaax et al.
2006/0167497	A1	7/2006	Armstrong et al.
2006/0167498	A1	7/2006	DiLorenzo
2006/0167501	A1	7/2006	Ben-David et al.
2006/0173493	A1	8/2006	Armstrong et al.
2006/0173508	A1	8/2006	Stone et al.
2006/0178691	A1	8/2006	Binmoeller
2006/0178706	A1	8/2006	Lisogurski et al.
2006/0190044	A1	8/2006	Libbus et al.
2006/0190053	A1	8/2006	Dobak
2006/0200208	A1	9/2006	Terry, Jr. et al.
2006/0200219	A1	9/2006	Thrope et al.
2006/0206155	A1	9/2006	Ben-David et al.
2006/0206158	A1	9/2006	Wu et al.
2006/0229677	A1	10/2006	Moffitt et al.
2006/0229681	A1	10/2006	Fischell
2006/0241697	A1	10/2006	Libbus et al.
2006/0241699	A1	10/2006	Libbus et al.
2006/0247719	A1	11/2006	Maschino et al.
2006/0247721	A1	11/2006	Maschino et al.
2006/0247722	A1	11/2006	Maschino et al.
2006/0259077	A1	11/2006	Pardo et al.
2006/0259084	A1	11/2006	Zhang et al.
2006/0259085	A1	11/2006	Zhang et al.
2006/0259107	A1	11/2006	Caparso et al.
2006/0271115	A1	11/2006	Ben-Ezra et al.
2006/0282121	A1	12/2006	Payne et al.
2006/0282131	A1	12/2006	Caparso et al.
2006/0282145	A1	12/2006	Caparso et al.
2006/0287678	A1	12/2006	Shafer
2006/0287679	A1	12/2006	Stone
2006/0292099	A1	12/2006	Milburn et al.
2006/0293720	A1	12/2006	DiLorenzo
2006/0293721	A1	12/2006	Tarver et al.
2006/0293723	A1	12/2006	Whitehurst et al.
2007/0016262	A1	1/2007	Gross et al.
2007/0016263	A1	1/2007	Armstrong et al.
2007/0021785	A1	1/2007	Inman et al.
2007/0021786	A1	1/2007	Parnis et al.
2007/0021814	A1	1/2007	Inman et al.
2007/0025608	A1	2/2007	Armstrong
2007/0027482	A1	2/2007	Parnis et al.
2007/0027483	A1	2/2007	Maschino et al.
2007/0027484	A1	2/2007	Guzman et al.
2007/0027486	A1	2/2007	Armstrong
2007/0027492	A1	2/2007	Maschino et al.
2007/0027496	A1	2/2007	Parnis et al.
2007/0027497	A1	2/2007	Parnis
2007/0027498	A1	2/2007	Maschino et al.
2007/0027499	A1	2/2007	Maschino et al.
2007/0027500	A1	2/2007	Maschino et al.
2007/0027504	A1	2/2007	Barrett et al.
2007/0055324	A1	3/2007	Thompson et al.
2007/0067004	A1	3/2007	Boveja et al.
2007/0083242	A1	4/2007	Mazgalev et al.
2007/0093434	A1	4/2007	Rossetti et al.
2007/0093870	A1	4/2007	Maschino
2007/0093875	A1	4/2007	Chavan et al.
2007/0100263	A1	5/2007	Merfeld
2007/0100377	A1	5/2007	Armstrong et al.
2007/0100378	A1	5/2007	Maschino
2007/0100380	A1	5/2007	Fukui
2007/0100392	A1	5/2007	Maschino et al.
2007/0106339	A1	5/2007	Errico et al.
2007/0112404	A1	5/2007	Mann et al.
2007/0118177	A1	5/2007	Libbus et al.
2007/0118178	A1	5/2007	Fukui
2007/0129767	A1	6/2007	Wahlstrand
2007/0129780	A1	6/2007	Whitehurst et al.
2007/0135846	A1	6/2007	Knudson et al.
2007/0135856	A1	6/2007	Knudson et al.
2007/0135857	A1	6/2007	Knudson et al.
2007/0135858	A1	6/2007	Knudson et al.
2007/0136098	A1	6/2007	Smythe et al.
2007/0142870	A1	6/2007	Knudson et al.
2007/0142871	A1	6/2007	Libbus et al.
2007/0142874	A1	6/2007	John
2007/0150006	A1	6/2007	Libbus et al.
2007/0150011	A1	6/2007	Meyer et al.
2007/0150021	A1	6/2007	Chen et al.
2007/0150027	A1	6/2007	Rogers
2007/0156180	A1	7/2007	Jaax et al.
2007/0198063	A1	8/2007	Hunter et al.
2007/0239243	A1	10/2007	Moffitt et al.
2007/0244522	A1	10/2007	Overstreet
2007/0250145	A1	10/2007	Kraus et al.
2007/0255320	A1	11/2007	Inman et al.
2007/0255333	A1	11/2007	Giftakis
2007/0255339	A1	11/2007	Torgerson
2008/0015659	A1	1/2008	Zhang
2008/0021517	A1	1/2008	Dietrich
2008/0021520	A1	1/2008	Dietrich
2008/0046055	A1	2/2008	Durand et al.
2008/0051852	A1	2/2008	Dietrich et al.
2008/0058871	A1	3/2008	Libbus et al.
2008/0103407	A1	5/2008	Bolea et al.
2008/0140138	A1	6/2008	Ivanova et al.
2008/0166348	A1	7/2008	Kupper et al.
2008/0183226	A1	7/2008	Buras et al.
2008/0183246	A1	7/2008	Patel et al.
2008/0195171	A1	8/2008	Sharma
2008/0208266	A1	8/2008	Lesser et al.
2008/0213331	A1	9/2008	Gelfand et al.
2008/0234780	A1	9/2008	Smith
2008/0234790	A1	9/2008	Bayer et al.
2008/0281197	A1	11/2008	Wiley et al.
2008/0281365	A1	11/2008	Tweden et al.
2008/0281372	A1	11/2008	Libbus et al.
2009/0012590	A1	1/2009	Inman et al.
2009/0048194	A1	2/2009	Aerssens et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2009/0076561 A1 3/2009 Libbus et al.
2009/0082832 A1 3/2009 Carbunaru et al.
2009/0088821 A1 4/2009 Abrahamson
2009/0105782 A1 4/2009 Mickle et al.
2009/0112291 A1 4/2009 Wahlstrand et al.
2009/0123521 A1 5/2009 Weber et al.
2009/0125076 A1 5/2009 Shuros et al.
2009/0125079 A1 5/2009 Armstrong et al.
2009/0131995 A1 5/2009 Sloan et al.
2009/0171405 A1 7/2009 Craig
2009/0177112 A1 7/2009 Gharib et al.
2009/0182388 A1 7/2009 Von Arx et al.
2009/0187231 A1 7/2009 Errico et al.
2009/0210042 A1 8/2009 Kowalczewski
2009/0248097 A1 10/2009 Tracey et al.
2009/0254143 A1 10/2009 Tweden et al.
2009/0275997 A1 11/2009 Faltys et al.
2009/0276019 A1 11/2009 Perez et al.
2009/0281593 A9 11/2009 Errico et al.
2009/0281594 A1 11/2009 King et al.
2009/0312817 A1 12/2009 Hogle et al.
2010/0003656 A1 1/2010 Kilgard et al.
2010/0010556 A1 1/2010 Zhao et al.
2010/0010571 A1 1/2010 Skelton et al.
2010/0010581 A1 1/2010 Goetz et al.
2010/0010603 A1 1/2010 Ben-David et al.
2010/0016746 A1 1/2010 Hampton et al.
2010/0042186 A1 2/2010 Ben-David et al.
2010/0063563 A1 3/2010 Craig
2010/0074934 A1 3/2010 Hunter
2010/0167937 A1 7/2010 Goldknopf et al.
2010/0191304 A1 7/2010 Scott
2010/0204766 A1 8/2010 Zdeblick et al.
2010/0215632 A1 8/2010 Boss et al.
2010/0219796 A1 9/2010 Kallmyer
2010/0241183 A1 9/2010 DiLorenzo
2010/0241195 A1 9/2010 Meadows et al.
2010/0241207 A1 9/2010 Bluger
2010/0249859 A1 9/2010 DiLorenzo
2010/0280500 A1 11/2010 Skelton et al.
2010/0280562 A1 11/2010 Pi et al.
2010/0280569 A1 11/2010 Bobillier et al.
2011/0004266 A1 1/2011 Sharma
2011/0009734 A1 1/2011 Foley et al.
2011/0042574 A1 2/2011 Nishino et al.
2011/0054569 A1 3/2011 Zitnik et al.
2011/0066208 A1 3/2011 Pasricha et al.
2011/0082515 A1 4/2011 Libbus et al.
2011/0092882 A1 4/2011 Firlik et al.
2011/0144717 A1 6/2011 Burton et al.
2011/0145588 A1 6/2011 Stubbs et al.
2011/0152967 A1 6/2011 Simon et al.
2011/0224749 A1 9/2011 Ben-David et al.
2011/0247620 A1 10/2011 Armstrong et al.
2011/0275927 A1 11/2011 Wagner et al.
2011/0301658 A1 12/2011 Yoo et al.
2011/0301667 A1 12/2011 Olson et al.
2011/0307027 A1 12/2011 Sharma et al.
2012/0053657 A1 3/2012 Parker et al.
2012/0065706 A1 3/2012 Vallapureddy et al.
2012/0179219 A1 7/2012 Kisker et al.
2012/0185009 A1 7/2012 Kornet et al.
2012/0185020 A1 7/2012 Simon et al.
2012/0296176 A1 11/2012 Herbst
2012/0302821 A1 11/2012 Burnett
2013/0013016 A1 1/2013 Diebold
2013/0018439 A1 1/2013 Chow et al.
2013/0066392 A1 3/2013 Simon et al.
2013/0066395 A1 3/2013 Simon et al.
2013/0071390 A1 3/2013 Stadheim et al.
2013/0150756 A1 6/2013 Vitek et al.
2013/0245718 A1 9/2013 Birkholz et al.
2013/0274831 A1 10/2013 Otto et al.
2013/0278226 A1 10/2013 Cong et al.
2013/0289385 A1* 10/2013 Lozano A61K 51/0491
424/1.73
2013/0317580 A1 11/2013 Simon et al.
2014/0046407 A1 2/2014 Ben-Ezra et al.
2014/0070761 A1 3/2014 Labbe et al.
2014/0105255 A1 4/2014 Kutner
2014/0206945 A1 7/2014 Liao
2014/0213926 A1 7/2014 Vaidyanathan
2014/0257425 A1 9/2014 Arcot-Krishnamurthy et al.
2014/0277260 A1 9/2014 Khalil et al.
2014/0288551 A1 9/2014 Bharmi et al.
2014/0324118 A1 10/2014 Simon et al.
2014/0330335 A1 11/2014 Errico et al.
2014/0371818 A1 12/2014 Bond et al.
2015/0018728 A1 1/2015 Gross et al.
2015/0119956 A1 4/2015 Libbus et al.
2015/0133717 A1 5/2015 Ghiron et al.
2015/0180271 A1 6/2015 Angara et al.
2015/0196767 A1 7/2015 Ahmed
2015/0233904 A1 8/2015 Nayak
2015/0241447 A1 8/2015 Zitnik et al.
2016/0089540 A1 3/2016 Bolea
2016/0250097 A9 9/2016 Tracey et al.
2016/0279435 A1 9/2016 Hyde et al.
2016/0331952 A1 11/2016 Faltys et al.
2016/0367808 A9 12/2016 Simon et al.
2017/0202467 A1 7/2017 Zitnik et al.
2017/0245379 A1 8/2017 Kang
2017/0254818 A1 9/2017 Haskins et al.
2017/0304621 A1 10/2017 Malbert et al.
2017/0361093 A1 12/2017 Yoo et al.
2018/0001096 A1 1/2018 Faltys et al.
2018/0021580 A1 1/2018 Tracey et al.
2018/0117320 A1 5/2018 Levine et al.
2018/0289970 A1 10/2018 Faltys et al.
2019/0010535 A1 1/2019 Pujol Onofre et al.
2019/0192847 A1 6/2019 Faltys et al.
2019/0275328 A1 9/2019 Zitnik et al.
2020/0078589 A1 3/2020 Simon et al.
2020/0330760 A1 10/2020 Levine et al.
2021/0251848 A1 8/2021 Tracey et al.
2021/0315505 A1 10/2021 Levine et al.
2021/0353949 A1 11/2021 Faltys et al.
2022/0040483 A1 2/2022 Levine et al.
2022/0072309 A9 3/2022 Levine et al.
2022/0118257 A1 4/2022 Huston et al.
2022/0193413 A1 6/2022 Levine et al.
2023/0117074 A1 4/2023 Zanos et al.
2023/0144580 A1 5/2023 Manogue
2023/0241387 A1 8/2023 Levine et al.
2023/0321445 A1 10/2023 Zanos et al.
2024/0215900 A1 7/2024 Levine et al.
2024/0216688 A1 7/2024 Zitnik et al.
2024/0299745 A1 9/2024 Levine et al.
2024/0307688 A1 9/2024 Levine

FOREIGN PATENT DOCUMENTS

CN 101578067 A 11/2009
CN 101868280 A 10/2010
CN 104220129 A 12/2014
CN 104602759 A 5/2015
DE 2628045 A1 1/1977
DE 3736664 A1 5/1989
DE 20316509 U1 4/2004
EP 0438510 B1 8/1996
EP 0726791 B1 6/2000
EP 1001827 B1 1/2004
EP 2213330 A2 8/2010
EP 2073896 B1 10/2011
GB 04133 2/1910
GB 2073428 A 10/1981
JP 2017502787 1/2017
KR 20050039445 A 4/2005
WO WO93/01862 A1 2/1993
WO WO97/30998 A1 8/1997
WO WO98/20868 A1 5/1998
WO WO00/27381 A2 5/2000
WO WO00/47104 A2 8/2000

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO01/00273	A1	1/2001
WO	WO01/08617	A1	2/2001
WO	WO01/89526	A1	11/2001
WO	WO02/44176	A1	6/2002
WO	WO02/057275	A1	7/2002
WO	WO03/072135	A2	9/2003
WO	WO2004/000413	A2	12/2003
WO	WO2004/064918	A1	8/2004
WO	WO2006/073484	A1	7/2006
WO	WO2006/076681	A2	7/2006
WO	WO2007/133718	A2	11/2007
WO	WO2010/005482	A1	1/2010
WO	WO2010/067360	A2	6/2010
WO	WO2010/118035	A2	10/2010
WO	WO2015/009907	A1	1/2015
WO	WO2016/134197	A1	8/2016

OTHER PUBLICATIONS

Gautron et al. Neurobiology of inflammation-associated anorexia; Frontiers in Neuroscience published: Jan. 8, 2010 vol. 3 | Article 59 doi: 10.3389/neuro.23.003.2009 (Year: 2010).*

Jacob et al.; Detrimental role of granulocyte-colony stimulating factor in neuromyelitis optica: clinical case and histological evidence; Multiple Sclerosis Journal; 18(12); pp. 1801-1803; Dec. 2012.

Levine et al.; U.S. Appl. No. 18/151,407 entitled "Control of vagal stimulation," filed Jan. 6, 2023.

Huston et al.; U.S. Appl. No. 18/355,401 entitled "Methods for reducing bleeding in hemophilia by vagus nerve stimualtion to prime platelets," filed Jul. 19, 2023.

Huston et al.; U.S. Appl. No. 17/784,805 entitled "Treating bleeding and bleeding disorders via high intensity focused ultrasound stimulation of the spleen," filed Jun. 13, 2022.

Zitnik et al.; U.S. Appl. No. 17/875,327 entitled "Batteryless Implantable Microstimulators," filed Jul. 27, 2022.

De Jonge et al.; Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway; Nature Immunology; 6(8); pp. 844-851; Aug. 2005.

Emery et al.; Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: switch-ra, a global, oberservational, comparative effectiveness study; Annals of the Rheumatic Diseases; 4(6); pp. 979-984; Jun. 2015.

Monaco et al.; Anti-TNF therapy:past,present, and future; International Immunology; 27(1); pp. 55-62; Jan. 2015.

Olofsson et al.; Single-pulse and unidirectional electrical activation of the cervical vagus nerve reduces tumor necrosis factor in endotoxemia; Bioelectronic Medicine; 2(1); pp. 37-42; Jun. 2015.

Rendas-Baum et al.; Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor-alpha inhibitors; Arthritis research and therapy; 13; R25; 15 pages; ; Feb. 2011.

Rosas-Ballina et al.; Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit Science; 334(6052); pp. 98-101; 10 pages; (Author Manuscript); Oct. 2011.

Vida et al.; Aplha 7-cholinergic receptor mediates vagal induction of splenic norepinephrine; Journal of Immunology; 186(7); pp. 4340-4346; 16 pages; (Author Manuscript); Apr. 2011.

Yang et al.; Acetylcholine inhibits LPS-induced MMP-9 production and ccell migration via the alpha7 nAChR-JAK2/STAT3 pathway in RAW264.7 cells; Cellular Physiology and Biochemistry; 36(5); pp. 2025-2038; (the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue) 2015.

Faltys et al.; U.S. Appl. No. 17/751,505 entitled "Implantable neurostimulator having power control and thermal regulation and methods of use," filed May 23, 2022.

Abraham, Coagulation abnormalities in acute lung injury and sepsis, Am. J. Respir. Cell Mol. Biol., vol. 22(4), pp. 401-404, Apr. 2000.

Aekerlund et al., Anti-inflammatory effects of a new tumour necrosis factor-alpha (TNF-Alpha) inhibitor (CNI-1493) in collagen-induced arthritis (CIA) in rats, Clinical & Experimental Immunology, vol. 115, No. 1, pp. 32-41, Jan. 1, 1999.

Anderson et al.; Reflex principles of immunological homeostasis; Annu. Rev. Immunol.; 30; pp. 313-335; Apr. 2012.

Antonica, A., et al., Vagal control of lymphocyte release from rat thymus, J. Auton. Nerv. Syst., vol. 48(3), pp. 187-197, Aug. 1994.

Asakura et al., Non-surgical therapy for ulcerative colitis, Nippon Geka Gakkai Zasshi, vol. 98, No. 4, pp. 431-437, Apr. 1997 (abstract only).

Beliavskaia et al.,"On the effects of prolonged stimulation of the peripheral segment of the vagus nerve . . . ," Fiziologicheskii Zhurnal SSSR Imeni I.M. Sechenova., vol. 52(11); p. 1315-1321, Nov. 1966.

Ben-Noun et al.; Neck circumference as a simple screening measure for identifying overweight and obese patients; Obesity Research; vol. 9; No. 8; pp. 470-477; Aug. 8, 2001.

Benoist, et al., "Mast cells in autoimmune disease" Nature., vol. 420(19): pp. 875-878, Dec. 2002.

Benthem et al.; Parasympathetic inhibition of sympathetic neural activity to the pancreas; Am.J.Physiol Endocrinol.Metab; 280(2); pp. E378-E381; Feb. 2001.

Bernik et al., Vagus nerve stimulation attenuates cardiac TNF production in endotoxic shock, (supplemental to Shock, vol. 15, 2001, Injury, inflammation and sepsis: laboratory and clinical approaches, Shock, Abstracts, 24th Annual Conference on Shock, Marco Island, FL, Jun. 9-12, 2001), Abstract No. 81.

Bernik et al., Vagus nerve stimulation attenuates endotoxic shock and cardiac TNF production, 87th Clinical Congress of the American College of Surgeons, New Orleans, LA, Oct. 9, 2001.

Bernik et al., Vagus nerve stimulation attenuates LPS-induced cardiac TNF production and myocardial depression in shock, New York Surgical Society, New York, NY, Apr. 11, 2001.

Bernik, et al., Pharmacological stimulation of the cholinergic anti-inflammatory pathway, The Journal of Experimental Medicine, vol. 195, No. 6, pp. 781-788, Mar. 18, 2002.

Besedovsky, H., et al., Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones, Science, vol. 233, No. 4764, pp. 652-654, Aug. 1986.

Bhattacharya, S.K. et al., Central muscarinic receptor subtypes and carrageenin-induced paw oedema in rats, Res. Esp. Med. vol. 191(1), pp. 65-76, Dec. 1991.

Bianchi et al., Suppression of proinflammatory cytokines in monocytes by a tetravalent guanylhydrazone, Journal of Experimental Medicine, vol. 183, pp. 927-936, Mar. 1996.

Biggio et al.; Chronic vagus nerve stimulation induces neuronal plasticity in the rat hippocampus; Int. J. Neurpsychopharmacol.; vol. 12; No. 9; pp. 1209-1221; Oct. 2009.

Blackwell, T. S. et al., Sepsis and cytokines: current status, Br. J. Anaesth., vol. 77(1), pp. 110-117, Jul. 1996.

Blum, A. et al., Role of cytokines in heart failure, Am. Heart J., vol. 135(2), pp. 181-186, Feb. 1998.

Boldyreff, Gastric and intestinal mucus, its properties and physiological importance, Acta Medica Scandinavica (journal), vol. 89, Issue 1-2, pp. 1-14, Jan./Dec. 1936.

Borovikova et al., Acetylcholine inhibition of immune response to bacterial endotoxin in human macrophages, Abstracts, Society for Neuroscience, 29th Annual Meeting, Miami Beach, FL, (Abs. No. 624.6); Oct. 23-28, 1999.

Borovikova et al., Efferent vagus nerve activity attenuates cytokine-mediated inflammation, Society for Neuroscience Abstracts, vol. 26, No. 102, Nov. 4-9, 2000 (abstract only).

Borovikova et al., Intracerebroventricular CNI-1493 prevents LPS-induced hypotension and peak serum TNF at a four-log lower dose than systemic treatment, 21st Annual Conference on Shock, San Antonio, TX, Jun. 14-17, 1998, Abstract No. 86.

Borovikova et al., Role of the efferent vagus nerve signaling in the regulation of the innate immune response to LPS, (supplemental to Shock, vol. 13, 2000, Molecular, cellular, and systemic pathobiologi-

(56) **References Cited**

OTHER PUBLICATIONS

cal aspects and therapeutic approaches, abstracts, 5th World Congress on Trauma, Shock inflammation and sepsis-pathophysiology, immune consequences and therapy, Feb. 29, 2000-Mar. 4, 2000, Munich, DE), Abstract No. 166.
Borovikova et al., Role of the vagus nerve in the anti-inflammatory effects of CNI-1493, the FASEB journal, vol. 14, No. 4, 2000 (Experimental Biology 2000, San Diego, CA, Apr. 15-18, 2000, Abstract No. 97.9).
Borovikova et al., Vagotomy blocks the protective effects of I.C.V. CNI-1493 against LPS-induced shock, (Supplemental to Shock, vol. 11, 1999, Molecular, cellular, and systemic pathobioloigal aspects and therapeutic approaches, abstacts and program, Fourth international Shock Congress and 22nd Annual Conference on Shock, Philadelphia, PA, Jun. 12-16, 1999), Abstract No. 277.
Borovikova, L. V., et al., Role of vagus nerve signaling in CNI-1493-mediated suppression of acute inflammation, Autonomic Neuroscience, vol. 85, No. 1-3, pp. 141-147, Dec. 20, 2000.
Borovikova, L. V., et al., Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin, Nature, vol. 405, No. 6785: pp. 458-462, May 25, 2000.
Bruchfeld et al.; Whole blood cytokine attenuation by cholinergic agonists ex vivo and relationship to vagus nerve activity in rheumatoid arthritis; J. Int. Med.; 268(1); pp. 94-101; Jul. 2010.
Bulloch et al.; Characterization of choline O-acetyltransferase (ChAT) in the BALB/C mouse spleen; Int.J.Neurosci.; 76(1-2); pp. 141-149; May 1994.
Bumgardner, G. L. et al., Transplantation and cytokines, Seminars in Liver Disease, vol. 19, No. 2, Thieme Medical Publishers; pp. 189-204, © 1999.
Burke et al., Bent pseudoknots and novel RNA inhibitors of type 1 human immunodeficiency virus (HIV-1) reverse transcriptase, J. Mol. Biol., vol. 264(4); pp. 650-666, Dec. 1996.
Bushby et al.; Centiles for adult head circumference; Archives of Disease in Childhood; vol. 67(10); pp. 1286-1287; Oct. 1992.
Cano et al.; Characterization of the central nervous system innervation of the rat spleen using viral transneuronal tracing; J.Comp Neurol.; 439(1); pp. 1-18; Oct. 2001.
Carteron, N. L., Cytokines in rheumatoid arthritis: trials and tribulations, Mol. Med. Today, vol. 6(8), pp. 315-323, Aug. 2000.
Cavaillon et al.; The pro-inflammatory cytokine casade; Immune Response in the Critically Ill; Springer-Verlag Berlin Hiedelberg; pp. 37-66; Jan. 21, 2002.
Cheyuo et al.; The parasympathetic nervous system in the quest for stroke therapeutics; J. Cereb. Blood Flow Metab.; 31(5); pp. 1187-1195; May 2011.
Cicala et al., "Linkage between inflammation and coagulation: An update on the molecular basis of the crosstalk," Life Sciences, vol. 62(20); pp. 1817-1824, Apr. 1998.
Clark et al.; Enhanced recognition memory following vagus nerve stimulation in human subjects; Nat. Neurosci., 2(1); pp. 94-98; Jan. 1999.
Cohen, "The immunopathogenesis of sepsis," Nature., vol. 420(6917): pp. 885-891, Dec. 2002.
Corcoran, et al., The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in humans: a preliminary report, NeuroImmunoModulation, vol. 12(5), pp. 307-309, Sep. 2005.
Crusz et al.; Inflammation and cancer; advances and new agents; Nature reviews Clinical Oncology; 12(10); pp. 584-596; doi: 10.1038/nrclinonc.2015.105; Jun. 30, 2015.
Dake; Chronic cerebrospinal venous insufficiency and multiple sclerosis: Hostory and background; Techniques Vasc. Intervent. Radiol.; 15(2); pp. 94-100; Jun. 2012.
Das, Critical advances in spticemia and septic shock, Critical Care, vol. 4, pp. 290-296, Sep. 7, 2000.
Del Signore et al; Nicotinic acetylcholine receptor subtypes in the rat sympathetic ganglion: pharmacological characterization, subcellular distribution and effect of pre- and postganglionic nerve crush; J.Neuropathol.Exp.Neurol.; 63(2); pp. 138-150; Feb. 2004.
Diamond et al.; Mapping the immunological homunculus; Proc. Natl. Acad. Sci. USA; 108(9); pp. 3461-3462; Mar. 1, 2011.
Dibbs, Z., et al., Cytokines in heart failure: pathogenetic mechanisms and potential treatment, Proc. Assoc. Am. Physicians, vol. 111, No. 5, pp. 423-428, Sep.-Oct. 1999.
Dinarello, C. A., The interleukin-1 family: 10 years of discovery, FASEB J., vol. 8, No. 15, pp. 1314-1325, Dec. 1994.
Dorr et al.; Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission; J. Pharmacol. Exp. Ther.; 318(2); pp. 890-898; Aug. 2006.
Doshi et al., Evolving role of tissue factor and its pathway inhibitor, Crit. Care Med., vol. 30, suppl. 5, pp. S241-S250, May 2002.
Elenkov et al.; Stress, corticotropin-releasing hormone, glucocorticoids, and the immune / inflammatory response: acute and chronic effects; Ann. N.Y. Acad. Sci.; 876; pp. 1-13; Jun. 22, 1999.
Ellington et al., In vitro selection of RNA molecules that bind specific ligands, Nature, vol. 346, pp. 818-822, Aug. 30, 1990.
Ellrich et al.; Transcutaneous vagus nerve stimulation; Eur. Neurological Rev.; 6(4); pp. 254-256; Winter 2011.
Engineer et al.; Directing neural plasticity to understand and treat tinnitus; Hear. Res.; 295; pp. 58-66; Jan. 2013.
Engineer et al.; Reversing pathological neural activity using targeted plasticity; Nature; 470(7332); pp. 101-104; Feb. 3, 2011 (Author Manuscript).
Esmon, The protein C pathway, Crit. Care Med., vol. 28, suppl. 9, pp. S44-S48, Sep. 2000.
Fields; New culprits in chronic pain; Scientific American; pp. 50-57; Nov. 2009.
Fleshner, M., et al., Thermogenic and corticosterone responses to intravenous cytokines (IL-1? and TNF-?) are attenuated by subdiaphragmatic vagotomy, J. Neuroimmunol., vol. 86(2), pp. 134-141, Jun. 1998.
Fox, D. A., Cytokine blockade as a new strategy to treat rheumatoid arthritis, Arch. Intern. Med., vol. 160, pp. 437-444, Feb. 28, 2000.
Fox, et al., Use of muscarinic agonists in the treatment of Sjorgren' syndrome, Clin. Immunol., vol. 101, No. 3; pp. 249-263, Dec. 2001.
Fujii et al.; Simvastatin regulates non-neuronal cholinergic activity in T lymphocytes via CD11a-mediated pathways; J. Neuroimmunol.; 179(1-2); pp. 101-107; Oct. 2006.
Gao et al.; Investigation of specificity of auricular acupuncture points in regulation of autonomic function in anesthetized rats; Autonomic Neurosc.; 138(1-2); pp. 50-56; Feb. 29, 2008.
Gattorno, M., et al., Tumor necrosis factor induced adhesion molecule serum concentrations in henoch-schoenlein purpura and pediatric systemic lupus erythematosus, J. Rheumatol., vol. 27, No. 9, pp. 2251-2255, Sep. 2000.
Gaykema, R. P., et al., Subdiaphragmatic vagotomy suppresses endotoxin-induced activation of hypothalamic corticotropin-releasing hormone neurons and ACTH secretion, Endocrinology, vol. 136, No. 10, pp. 4717-4720, Oct. 1995.
Ghelardini et al., S-(-)-ET 126: A potent and selective M1 antagonist in vitro and in vivo, Life Sciences, vol. 58, No. 12, pp. 991-1000, Feb. 1996.
Ghia, et al., The vagus nerve: a tonic inhibitory influence associated with inflammatory bowel disease in a murine model, Gastroenterology, vol. 131, No. 4, pp. 1122-1130, Oct. 2006.
Giebelen, et al., Stimulation of ?7 cholinergic receptors inhibits lipopolysaccharide-induced neutrophil recruitment by a tumor necrosis factor?-independent mechanism, Shock, vol. 27, No. 4, pp. 443-447, Apr. 2007.
Goyal et al., Nature of the vagal inhibitory innervation to the lower esophageal sphincter, Journal of Clinical Investigation, vol. 55, pp. 1119-1126, May 1975.
Gracie, J. A., et al., A proinflammatory role for IL-18 in rheumatoid arthritis, J. Clin. Invest., vol. 104, No. 10, pp. 1393-1401, Nov. 1999.
Granert et al., Suppression of macrophage activation with CNI-1493 increases survival in infant rats with systemic haemophilus influenzae infection, Infection and Immunity, vol. 68, No. 9, pp. 5329-5334, Sep. 2000.
Green et al., Feedback technique for deep relaxation, Psycophysiology, vol. 6, No. 3, pp. 371-377, Nov. 1969.

(56) **References Cited**

OTHER PUBLICATIONS

Gregory et al., Neutrophil-kupffer-cell interaction in host defenses to systemic infections, Immunology Today, vol. 19, No. 11, pp. 507-510, Nov. 1998.

Groves et al.; Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat; Neuroscience Letters; 379(3); pp. 174-179; May 13, 2005.

Guarente, Leonard, Ph. D.; Sirtuins, Aging, and Medicine; N Engl J Med ; vol. 364:pp. 2235-2244; Jun. 2011.

Guslandi, M., Nicotine treatment for ulcerative colitis, Br. J. Clin. Pharmacol., vol. 48(4), pp. 481-484, Oct. 1999.

Hansson, E.; Could chronic pain and spread of pain sensation be induced and maintained by glial activation?. Acta Physiologica, vol. 187, Issue 1-2; pp. 321R327, May/Jun. 2006.

Harrison's Principles of Internal Medicine, 13th Ed., pp. 511-515 and 1433-1435, Mar. 1994.

Hatton et al.; Vagal nerve stimulation: overview and implications for anesthesiologists; Int'l Anesthesia Research Society; vol. 103; No. 5; pp. 1241-1249; Nov. 2006.

Hirano, T., Cytokine suppresive agent improves survival rate in rats with acute pancreatitis of closed duodenal loop, J. Surg. Res., vol. 81, No. 2, pp. 224-229, Feb. 1999.

Hirao et al., The limits of specificity: an experimental analysis with RNA aptamers to MS2 coat protein variants, Mol. Divers., vol. 4, No. 2, pp. 75-89, 1999 (Accepted Jan. 13, 1999).

Hoffer et al.; Implantable electrical and mechanical interfaces with nerve and muscle; Annals of Biomedical Engineering; vol. 8; pp. 351-360; Jul. 1980.

Holladay et al., Neuronal nicotinic acetylcholine receptors as targets for drug discovery, Journal of Medicinal Chemistry, 40(26), pp. 4169-4194, Dec. 1997.

Hommes, D. W. et al., Anti- and Pro-inflammatory cytokines in the pathogenesis of tissue damage in Crohn's disease, Current Opinion in Clinical Nutrition and Metabolic Care, vol. 3(3), pp. 191-195, May 2000.

Hsu, et al., Analysis of efficiency of magnetic stimulation, IEEE Trans. Biomed. Eng., vol. 50(11), pp. 1276-1285, Nov. 2003.

Hsu, H. Y., et al., Cytokine release of peripheral blood monoculear cells in children with chronic hepatitis B virus infection, J. Pediatr. Gastroenterol., vol. 29, No. 5, pp. 540-545, Nov. 1999.

Hu, et al., The effect of norepinephrine on endotoxin-mediated macrophage activation, J. Neuroimmunol., vol. 31(1), pp. 35-42, Jan. 1991.

Huston et al.; Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis; J. Exp. Med. 2006; vol. 203, No. 7; pp. 1623-1628; Jun. 19, 2006.

Huston et al.; Transcutaneous vagus nerve stimulation reduces serum high mobility group box 1 levels and improves survival in murine sepsis; Crit. Care Med.; 35(12); pp. 2762-2768; Dec. 2007.

Hutchinson et al.; Proinflammatory cytokines oppose opioid induced acute and chronic analgesia; Brain Behav Immun.; vol. 22; No. 8; pp. 1178-1189; Nov. 2008.

Ilton et al., "Differential expression of neutrophil adhesion molecules during coronary artery surgery with cardiopulmonary bypass" Journal of Thoracic and Cardiovascular Surgery, Mosby-Year Book, inc., St. Louis, Mo, US, pp. 930-937, Nov. 1, 1999.

Jaeger et al., The structure of HIV-1 reverse transcriptase complexed with an RNA pseudoknot inhibitor, The EMBO Journal, 17(15), pp. 4535-4542, Aug. 1998.

Jander, S. et al., Interleukin-18 is induced in acute inflammatory demyelinating polymeuropathy, J. Neuroimmunol., vol. 114, pp. 253-258, Mar. 2001.

Joshi et al., Potent inhibition of human immunodeficiency virus type 1 replection by template analog reverse transcriptase , J. Virol., 76(13), pp. 6545-6557, Jul. 2002.

Kalishevskaya et al. "The character of vagotomy-and atropin-induced hypercoagulation," Sechenov Physiological Journal of the USSR, 65(3): pp. 398-404, Mar. 1979.

Kalishevskaya et al.; Nervous regulation of the fluid state of the blood; Usp. Fiziol. Nauk;,vol. 13; No. 2; pp. 93-122; Apr.-Jun. 1982.

Kanai, T. et al., Interleukin-18 and Crohn's disease, Digestion, vol. 63, suppl. 1, pp. 37-42; 2001 (year of pub. sufficiently earlier than effective US filing date and any foreign priority date).

Katagiri, M., et al., Increased cytokine production by gastric mucosa in patients with helicobacter pylori infection, J. Clin, Gastroenterol., vol. 25, Suppl. 1, pp. S211-S214, 1997.

Katsavos et al.; Biomarkers in multiple sclerosis: an up-to-date overview; Multiple Sclerosis International; vol. 2013, Article ID 340508, 20 pages; 2013 (year of pub. sufficiently earlier than effective US filing date and any foreign priority date).

Kawahara et al.; SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span.; Cell. : vol. 136; No. 1; pp. 62-74; Jan. 2009.

Kawashima, et al., Extraneuronal cholinergic system in lymphocytes, Pharmacology & Therapeutics, vol. 86, pp. 29-48, Apr. 2000.

Kees et al; Via beta-adrenoceptors, stimulation of extrasplenic sympathetic nerve fibers inhibits lipopolysaccharide-induced TNF secretion in perfused rat spleen; J.Neuroimmunol.; 145(1-2); pp. 77-85; Dec. 2003.

Kensch et al., HIV-1 reverse transcriptase-pseudoknot RNA aptamer interaction has a binding affinity in the low picomolar range coupled with high specificity, J. Biol. Chem., 275(24), pp. 18271-18278, Jun. 16, 2000.

Khatun, S., et al., "Induction of hypercoagulability condition by chronic localized cold stress in rabbits," Thromb. and Haemost., 81(3): pp. 449-455, Mar. 1999.

Kimball, et al., Levamisole causes differential cytokine expression by elicited mouse peritoneal macrophases, Journal of Leukocyte Biology, vo. 52, No. 3, pp. 349-356, Sep. 1992 (abstract only).

Kimmings, A. N., et al., Systemic inflammatory response in acute cholangitis and after subsequent treatment, Eur. J. Surg., vol. 166, pp. 700-705, Sep. 2000.

Kirchner et al.; Left vagus nerve stimulation suppresses experimentally induced pain; Neurology; vol. 55; pp. 1167-1171; Oct. 2000.

Kokkula, R. et al., Successful treatment of collagen-induced arthritis in mice and rats by targeting extracellular high mobility group box chromosomal protein 1 activity, Arthritis Rheum., 48(7), pp. 2052-2058, Jul. 2003.

Koopman et al.; Pilot study of stimulation of the cholinergic anti-inflammatory pathway with an implantable vagus nerve stimulation device in patients with rheumatoid arthritis; Arth. Rheum.; 64(10 suppl.); pp. S195; Oct. 2012.

Koopman et al.; Pilot study of stimulation of the cholinergic anti-inflammatory pathway with an implantable vagus nerve stimulation device in patients with rheumatoid arthritis; 2012 ACR/ARHP Annual Meeting; Abstract No. 451; 4 pages; retrieved from the internet (https://acrabstracts.org/abstract/pilot-study-of-stimulation-of-the-cholinergic-anti-inflammatory-pathway-with-an-implantable-vagus-nerve-stimulation-device-in-patients-with-rheumatoid-arthritis); (Abstract Only); on Sep. 24, 2020.

Koopman et al.; THU0237 first-in-human study of vagus nerve stimulation for rheumatoid arthritis: clinical and biomarker results through day 84; Annals of the Rheumatic Diseases; 72(Suppl 3):A245; Jun. 1, 2013 (Abstract Only).

Krarup et al; Conduction studies in peripheral cat nerve using implanted electrodes: I. methods and findings in controls; Muscle & Nerve; vol. 11; pp. 922-932; Sep. 1988.

Kudrjashov, et al. "Reflex nature of the physiological anticoagulating system," Nature, vol. 196(4855): pp. 647-649; Nov. 17, 1962.

Kumins, N. H., et al., Partial hepatectomy reduces the endotoxin-induced peak circulating level of tumor necrosis factor in rats, Shock, vol. 5, No. 5, pp. 385-388, May 1996.

Kuznik, "Role of the vascular wall in the process of hemostatis," Usp Sovrem Biol., vol. 75(1): pp. 61-85; 1973 (the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue).

Kuznik, et al., "Blood Coagulation in stimulation of the vagus nerve in cats," Blull. Eskp. Biol. Med., vol. 78(7): pp. 7-9; 1974 (the year

(56) **References Cited**

OTHER PUBLICATIONS

of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue).
Kuznik, et al., "Heart as an efferent regulator of the process of blood coagulation and fibrinolysis," Kardiologiia, vol. 13(3): pp. 10-17; 1973 (the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue).
Kuznik, et al., "Role of the heart and vessels in regulating blood coagulation and fibrinolysis," Kagdiologiia, vol. 13(4): pp. 145-154, Apr. 1973.
Kuznik, et al., "Secretion of blood coagulation factors into saliva under conditions of hypo-and hypercoagulation," Voprosy Meditsinskoi Khimil, vol. 19(1): pp. 54-57; 1973(the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue).
Kuznik, et al., "The dynamics of procoagulatible and fibrinolytic activities during electrical stimulation of peripheral nerves," Sechenov Physiological Journal of the USSR, vol. 65; No. 3: pp. 414-420, Mar. 1979.
Kuznik, et al., "The role of the vascular wall in the mechanism of control of blood coagulation and fibrinolysis on stimulation of the vagus nerve," Cor Vasa, vol. 17(2): pp. 151-158; 1975 (the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue).
Lang, et al., "Neurogienic control of cerebral blood flow," Experimental Neurology, 43(1): pp. 143-161, Apr. 1974.
Lee, H. G., et al., Peritoneal lavage fluids stimulate NIH3T3 fibroblast proliferation and contain increased tumour necrosis factor and IL6 in experimental silica-induced rat peritonitis, Clin. Exp. Immunol., vol. 100, pp. 139-144, Apr. 1995.
LeNovere, N. et al., Molecular evolution of the nicotinic acetylcholine receptor: an example of multigene family in excitable cells, J. Mol. Evol., 40, pp. 155-172, Feb. 1995.
Leonard, S. et al., Neuronal nicotinic receptors: from structure to function, Nicotine & Tobacco Res. 3:203-223, Aug. 2001.
Lips et al.; Coexpression and spatial association of nicotinic acetylcholine receptor subunits alpha7 and alpha10 in rat sympathetic neurons; J.Mol.Neurosci.; 30; pp. 15-16; Feb. 2006.
Lipton, J. M. et al.; Anti-inflammatory actions of the neuroimmunomodulator ?-MSH, Immunol. Today, vol. 18, pp. 140-145, Mar. 1997.
Loeb et al.; Cuff electrodes for chronic stimulation and recording of peripheral nerve activity; Journal of Neuroscience Methods; vol. 64; pp. 95-103; Jan. 1996.
Mayo Clinic; The factsheet of vagus nerve stimulation from the Mayo Clinic website: www.mayoclinic.org/tests-procedures/vagus-nerve-sti mulation/about/pac-20384565; retrieved from the internet on Sep. 28, 2021.
Madretsma, G. S., et al., Nicotine inhibits the in vitro production of interleukin 2 and tumour necrosis factor-alpha by human monocuclear cells, Immunopharmacology, vol. 35, No. 1, pp. 47-51, Oct. 1996.
Manta et al.; Optimization of vagus nerve stimulation parameters using the firing activity of serotonin neurons in the rat dorsal raphe; European Neuropsychopharmacology; vol. 19; pp. 250-255; Jan. 2009 (doi: 10.1016/j.euroneuro.2008.12.001).
Martindale: The Extra Pharmacopoeia; 28th Ed. London; The Pharmaceutical Press; pp. 446-485; © 1982.
Martiney et al., Prevention and treatment of experimental autoimmune encephalomyelitis by CNI-1493, a macrophage-deactivating agent, Journal of Immunology, vol. 160, No. 11, pp. 5588-5595, Jun. 1, 1998.
McGuinness, P. H., et al., Increases in intrahepatic CD68 positive cells, MAC387 positive cells, and proinflammatory cytokines (particulary interleukin 18) in chronic hepatitis C infection, Gut, vol. 46(2), pp. 260-269, Feb. 2000.
Miguel-Hidalgo, J.J.; The role of glial cells in drug abuse; Current Drug Abuse Reviews; vol. 2; No. 1; pp. 76-82; Jan. 2009.
Milligan et al.; Pathological and protective roles of glia in chronic pain; Nat Rev Neurosci.; vol. 10; No. 1; pp. 23-26; Jan. 2009.
Minnich et al.; Anti-cytokine and anti-inflammatory therapies for the treatment of severe sepsis: progress and pitfalls; Proceedings of the Nutrition Society; vol. 63(3); pp. 437-441; Aug. 2004.
Mishchenko, et al., "Coagulation of the blood and fibrinolysos in dogs during vagal stimulation," Sechenov Physiological Journal of the USSR, vol. 61(1): pp. 101-107, 1975.
Mishchenko, "The role of specific adreno-and choline-receptors of the vascular wall in the regulation of blood coagulation in the stimulation of the vagus nerve," Biull. Eskp. Biol. Med., vol. 78(8): pp. 19-22, 1974.
Molina et al., CNI-1493 attenuates hemodynamic and pro-inflammatory responses to LPS, Shock, vol. 10, No. 5, pp. 329-334, Nov. 1998.
Nadol et al., "Surgery of the Ear and Temporal Bone," Lippinkott Williams & Wilkins, 2nd Ed., 2005, (Publication date: Sep. 21, 2004), p. 580.
Nagashima et al., Thrombin-activatable fibrinolysis inhibitor (TAFI) deficiency is compatible with murine life, J. Clin. Invest., 109, pp. 101-110, Jan. 2002.
Nathan, C. F., Secretory products of macrophages, J. Clin. Invest., vol. 79(2), pp. 319-326, Feb. 1987.
Navalkar et al.; Irbesartan, an angiotensin type 1 receptor inhibitor, regulates markers of inflammation in patients with premature atherosclerosis; Journal of the American College of Cardiology; vol. 37; No. 2; pp. 440-444; Feb. 2001.
Navzer et al.; Reversing pathological neural activity using targeted plasticity; Nature; 470(7332); pp. 101-104; Feb. 3, 2011.
Neuhaus et al.; P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder; J. Affect. Disord.; 100(1-3); pp. 123-128; Jun. 2007.
Noguchi et al., Increases in Gastric acidity in response to electroacupuncture stimulation of hindlimb of anesthetized rats, Jpn. J. Physiol., 46(1), pp. 53-58, Feb. 1996.
Norton, Can ultrasound be used to stimulate nerve tissue, BioMedical Engineering OnLine, 2(1), pp. 6, Mar. 4, 2003.
Olofsson et al.; Rethinking inflammation: neural circuits in the regulation of immunity; Immunological Reviews; 248(1); pp. 188-204; Jul. 2012.
Oshinsky et al.; Non-invasive vagus nerve stimulation as treatment for trigeminal allodynia; Pain; 155(5); pp. 1037-1042; May 2014.
Palmblad et al., Dynamics of early synovial cytokine expression in rodent collagen-induced arthritis: a thereapeutic study unding a macrophage-deactivation compound, American Journal of Pathology, vol. 158, No. 2, pp. 491-500, Feb. 2, 2001.
Pateyuk, et al., "Treatment of Botkin's disease with heparin," Klin. Med., vol. 51(3): pp. 113-117, Mar. 1973.
Pavlov et al; Controlling inflammation: the cholinergic anti-inflammatory pathway; Biochem. Soc. Trans.; 34(Pt 6); pp. 1037-1040; Dec. 2006.
Pavlov et al.; The cholinergic anti-inflammatory pathway; Brain, Behavior, and Immunity; 19; p. 493-499; Nov. 2005.
Palov et al.; The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation; Molecular Medicine; 9(5); pp. 125-134; May 2003.
Payne, J. B. et al., Nicotine effects on PGE2 and IL-1 beta release by LPS-treated human monocytes, J. Perio. Res., vol. 31, No. 2, pp. 99-104, Feb. 1996.
Peuker; The nerve supply of the human auricle; Clin. Anat.; 15(1); pp. 35-37; Jan. 2002.
Pongratz et al.; The sympathetic nervous response in inflammation; Arthritis Research and Therapy; 16(504); 12 pages; retrieved from the internet (http://arthritis-research.com/content/16/6/504) ; Jan. 2014.
Prystowsky, J. B. et al., Interleukin-1 mediates guinea pig gallbladder inflammation in vivo, J. Surg. Res., vol. 71, No. 2, pp. 123-126, Aug. 1997.
Pulkki, K. J., Cytokines and cardiomyocyte death, Ann. Med., vol. 29(4), pp. 339-343, Aug. 1997.

(56) **References Cited**

OTHER PUBLICATIONS

Pullan, R. D., et al., Transdermal nicotine for active ulcerative colitis, N. Engl. J. Med., vol. 330, No. 12, pp. 811-815, Mar. 24, 1994.
Pulvirenti et al; Drug dependence as a disorder of neural plasticity:focus on dopamine and glutamate; Rev Neurosci.; vol. 12; No. 2; pp. 141-158; Apr./Jun. 2001.
Rahman et al.; Mammalian Sirt 1: Insights on its biological functions; Cell Communications and Signaling; vol. 9; No. 11; pp. 1-8; May 2011.
Rayner, S. A. et al., Local bioactive tumour necrosis factor (TNF) in corneal allotransplantation, Clin. Exp. Immunol., vol. 122, pp. 109-116, Oct. 2000.
Reale et al.; Treatment with an acetylcholinesterase inhibitor in alzheimer patients modulates the expression and production of the pro-inflammatory and anti-inflammatory cytokines; J. Neuroimmunology: 148(1-2); pp. 162-171; Mar. 2004.
Rinner et al.; Rat lymphocytes produce and secrete acetylcholine in dependence of differentiation and activation; J.Neuroimmunol.; 81(1-2); pp. 31-37; Jan. 1998.
Robinson et al.; Studies with the Electrocardiogram the Action of the Vagus Nerve on the Human Heart; J Exp Med; 14(3):217-234; Sep. 1911.
Romanovsky, A. A., et al., The vagus nerve in the thermoregulatory response to systemic inflammation, Am. J. Physiol., vol. 273, No. 1 (part 2), pp. R407-R413, Jul. 1, 1997.
Saghizadeh et al.; The expression of TNF? by human muscle; J. Clin. Invest.; vol. 97; No. 4; pp. 1111-1116; Feb. 15, 1996.
Saindon et al.; Effect of cervical vagotomy on sympathetic nerve responses to peripheral interleukin-1beta; Auton.Neuroscience Basic and Clinical; 87; pp. 243-248; Mar. 23, 2001.
Saito, Involvement of muscarinic M1 receptor in the central pathway of the serotonin-induced bezold-jarisch reflex in rats, J. Autonomic Nervous System, vol. 49, pp. 61-68, Sep. 1994.
Sandborn, W. J., et al., Transdermal nicotine for mildly to moderately active ulcerative colitis, Ann. Intern. Med, vol. 126, No. 5, pp. 364-371, Mar. 1, 1997.
Sato, E., et al., Acetylcholine stimulates alveolar macrophages to release inflammatory cell chemotactic activity, Am. J. Physiol., vol. 274, pp. L970-L979, Jun. 1998.
Sato, K.Z., et al., Diversity of mRNA expression for muscarinic acetylcholine receptor subtypes and neuronal nicotinic acetylcholine receptor subunits in human mononuclear leukosytes and leukemic cell lines, Neuroscience Letters, vol. 266, pp. 17-20, Apr. 30, 1999.
Scheinman, R. I., et al., Role of transcriptional activation of 1?B? in mediation of immunosuppression by glucocorticoids, Science, vol. 270, No. 5234, pp. 283-286, Oct. 13, 1995.
Schneider et al., High-affinity ssDNA inhibitors of the review transcriptase of type 1 human immunodeficiency virus, Biochemistry, 34(29), pp. 9599-9610, Jul. 1995.
Shafer, Genotypic testing for human immunodeficiency virus type 1 drug resistance, Clinical Microbiology Reviews, vol. 15, pp. 247-277, Apr. 2002.
Shapiro et al.; Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery; Thromb Haemost; vol. 80(5); pp. 773-778; Nov. 1998.
Sher, M. E., et al., The influence of cigarette smoking on cytokine levels in patients with inflammatory bowel disease, Inflamm. Bowel Dis., vol. 5, No. 2, pp. 73-78, May 1999.
Shi et al.; Effects of efferent vagus nerve excitation on inflammatory response in heart tissue in rats with endotoxemia; vol. 15, No. 1; pp. 26-28; Jan. 2003 (Eng. Abstract).
Snyder et al., Correction of hemophilia B in canine and murine models using recombinant adeno-associated viral vectors; Nature Medicine, 5(1), pp. 64-70, Jan. 1999.
Sokratov, et al. "The role of choline and adrenegic structures in regulation of renal excretion of hemocoagulating compounds into the urine," Sechenov Physiological Journal of the USSR, vol. 63(12): pp. 1728-1732, 1977.
Stalcup et al., Endothelial cell functions in the hemodynamic responses to stress, Annals of the New York Academy of Sciences, vol. 401, pp. 117-131, Dec. 1982.
Steinlein, New functions for nicotine acetylcholine receptors?, Behavioural Brain Res., vol. 95(1), pp. 31-35, Sep. 1998.
Sternberg, E. M., Perspectives series: cytokines and the brain 'neural-immune interactions in health and disease,' J. Clin. Invest., vol. 100, No. 22, pp. 2641-2647, Dec. 1997.
Stevens et al.; The anti-inflammatory effect of some immunosuppressive agents; J. Path.; 97(2); pp. 367-373; Feb. 1969.
Strojnik et al.; Treatment of drop foot using and implantable peroneal underknee stimulator; Scand. J. Rehab. Med.; vol. 19(1); pp. 37R43; Dec. 1986.
Strowig et al.; Inflammasomes in health and disease; Nature; vol. 481; pp. 278-286; doi: 10.1038/nature10759; Jan. 19, 2012.
Sugano et al., Nicotine inhibits the production of inflammatory mediators in U937 cells through modulation of nuclear factor-kappaß activation, Biochemical and Biophysical Research Communications, vol. 252, No. 1, pp. 25-28, Nov. 9, 1998.
Suter et al.; Do glial cells control pain?; Neuron Glia Biol.; vol. 3; No. 3; pp. 255-268; Aug. 2007.
Swick et al.; Locus coeruleus neuronal activity in awake monkeys: relationship to auditory P300-like potentials and spontaneous EEG. Exp. Brain Res.: 101(1); pp. 86-92; Sep. 1994.
Sykes, et al., An investigation into the effect and mechanisms of action of nicotine in inflammatory bowel disease, Inflamm. Res., vol. 49, pp. 311-319, Jul. 2000.
Takeuchi et al., A comparison between chinese blended medicine "Shoseiryuto" tranilast and ketotifen on the anit-allergic action in the guinea pigs, Allergy, vol. 34, No. 6, pp. 387-393, Jun. 1985 (eng. abstract).
Tekdemir et al.; A clinico-anatomic study of the auricular branch of the vagus nerve and arnold's ear-cough reflex; Surg. Radiol. Anat.; 20(4); pp. 253-257; Mar. 1998.
Toyabe, et al., Identification of nicotinic acetylcholine receptors on lymphocytes in the periphery as well as thymus in mice, Immunology, vol. 92(2), pp. 201-205, Oct. 1997.
Tracey et al., Mind over immunity, Faseb Journal, vol. 15, No. 9, pp. 1575-1576, Jul. 2001.
Tracey, K. J. et al., Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia; Nature, 330: pp. 662-664, Dec. 23, 1987.
Tracey, K. J. et al., Physiology and immunology of the cholinergic antiinflammatory pathway; J Clin Invest.; vol. 117: No. 2; pp. 289-296; Feb. 2007.
Tracey, K. J. et al., Shock and tissue injury induced by recombinant human cachectin, Science, vol. 234, pp. 470-474, Oct. 24, 1986.
Tracey, K. J.; Reflex control of immunity; Nat Rev Immunol; 9(6); pp. 418-428; Jun. 2009.
Tracey, K.J., The inflammatory reflex, Nature, vol. 420, pp. 853-859, Dec. 19-26, 2002.
Tsutsui, H., et al., Pathophysiolocical roles of interleukin-18 in inflammatory liver diseases; Immunol. Rev., 174:192-209, Apr. 2000.
Tuerk et al., RNA pseudoknots that inhibit human immunodeficiency virus type 1 reverse transcriptase; Proc. Natl. Acad. Sci. USA, 89, pp. 6988-6992, Aug. 1992.
Tuerk et al., Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase; Science, 249(4968), pp. 505-510, Aug. 3, 1990.
Van Der Horst et al.; Stressing the role of FoxO proteins in lifespan and disease; Nat Rev Mol Cell Biol.; vol. 8; No. 6; pp. 440-450; Jun. 2007.
Van Dijk, A. P., et al., Transdermal nictotine inhibits interleukin 2 synthesis by mononuclear cells derived from healthy volunteers, Eur. J. Clin. Invest, vol. 28, pp. 664-671, Aug. 1998.
Vanhoutte, et al., Muscarinic and beta-adrenergic prejunctional modulation of adrenergic neurotransmission in the blood vessel wall, Gen Pharmac., vol. 14(1), pp. 35-37, Jan. 1983.
VanWesterloo, et al., The cholinergic anti-inflammatory pathway regulates the host response during septic peritonitis, The Journal of Infectious Diseases, vol. 191, pp. 2138-2148, Jun. 15, 2005.

(56) **References Cited**

OTHER PUBLICATIONS

Ventureyra, Transcutaneous vagus nerve stimulation for partial onset seizure therapy, Child's Nerv Syst, vol. 16(2), pp. 101-102, Feb. 2000.
Vijayaraghavan, S.; Glial-neuronal interactions—implications for plasticity anddrug addictionl AAPS J.; vol. 11; No. 1; pp. 123-132; Mar. 2009.
Villa et al., Protection against lethal polymicrobial sepsis by CNI-1493, an inhibitor of pro-inflammatory cytokine synthesis, Journal of Endotoxin Research, vol. 4, No. 3, pp. 197-204, Jun. 1997.
Von Känel, et al., Effects of non-specific ?-adrenergic stimulation and blockade on blood coagulation in hypertension, J. Appl. Physiol., vol. 94, pp. 1455-1459, Apr. 2003.
Von Känel, et al., Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo, Eur. J. Haematol., vol. 65: pp. 357-369, Dec. 2000.
Walland et al., Compensation of muscarinic brochial effects of talsaclidine by concomitant sympathetic activation in guinea pigs; European Journal of Pharmacology, vol. 330(2-3), pp. 213-219, Jul. 9, 1997.
Wang et al; Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation; Nature; 421; 384-388; Jan. 23, 2003.
Wang, H., et al., HMG-1 as a late mediator of endotoxin lethality in mice, Science, vol. 285, pp. 248-251, Jul. 9, 1999.
Waserman, S. et al., TNF-? dysregulation in asthma: relationship to ongoing corticosteroid therapy, Can. Respir. J., vol. 7, No. 3, pp. 229-237, May-Jun. 2000.
Watanabe, H. et al., The significance of tumor necrosis factor (TNF) levels for rejection of joint allograft, J. Reconstr. Microsurg., vol. 13, No. 3, pp. 193-197, Apr. 1997.
Wathey, J.C. et al., Numerical reconstruction of the quantal event at nicotinic synapses; Biophys. J., vol. 27: pp. 145-164, Jul. 1979.
Watkins, L.R. et al., Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication, Neurosci. Lett., vol. 183(1-2), pp. 27-31, Jan. 1995.
Watkins, L.R. et al., Implications of immune-to-brain communication for sickness and pain, Proc. Natl. Acad. Sci. U.S.A., vol. 96(14), pp. 7710-7713, Jul. 6, 1999.
Webster's Dictionary, definition of "intrathecal", online version accessed Apr. 21, 2009.
Weiner, et al., "Inflammation and therapeutic vaccination in CNS diseases," Nature., vol. 420(6917): pp. 879-884, Dec. 19-26, 2002.
Westerheide et al.; Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1.; Science; Vo. 323; No. 5717; pp. 1063-1066; Feb. 2009.
Whaley, K. et al., C2 synthesis by human monocytes is modulated by a nicotinic cholinergic receptor, Nature, vol. 293, pp. 580-582, Oct. 15, 1981.
Woiciechowsky, C. et al., Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury, Nature Med., vol. 4, No. 7, pp. 808-813, Jul. 1998.
Yeh, S.S. et al., Geriatric cachexia: the role of cytokines, Am. J. Clin. Nutr., vol. 70(2), pp. 183-197, Aug. 1999.
Yu et al.; Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve: a non-invasive approach to treat the initial phase of atrial fibrillation; Heart Rhythm; 10(3); pp. 428-435; Mar. 2013.
Zamotrinsky et al.; Vagal neurostimulation in patients with coronary artery disease; Auton. Neurosci.; 88(1-2); pp. 109-116; Apr. 2001.
Zhang et al., Tumor necrosis factor, The Cytokine Handbook, 3rd ed., Ed. Thompson, Academic Press, pp. 517-548, Jul. 1, 1998.
Zhang et al.; Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model; Circulation Heart Fail.; 2; pp. 692-699; Nov. 2009.
Zhang et al.; Roles of SIRT1 in the acute and restorative phases following induction of inflammation.; J Biol Chem.; vol. 285; No. 53; pp. 41391-401; Dec. 2010.
Zhao et al.; Transcutaneous auricular vagus stimulation protects endotoxemic rat from lipopolysaccharide-induced inflammation; Evid. Based Complement Alternat. Med.; vol. 2012; Article ID 627023; 10 pages; Dec. 29, 2012.
Zitnik et al.; Treatment of chronic inflammatory diseases with implantable medical devices; Cleveland Clinic Journal of Medicine; 78(Suppl 1); pp. S30-S34; Aug. 2011.
Manogue; U.S. Appl. No. 17/578,339 entitled "Methods and apparatuses for reducing bleeding via coordinated trigeminal and vagal nerve stimulation," filed Jan. 18, 2022.
Faltys et al.; U.S. Appl. No. 17/700,415 entitled "Systems and methods for establishing a nerve block," filed Mar. 21, 2022.
Yang et al.; Axon myelination and electrical stimulation in a microfluidic, compartmentalized cell culture platform; Neuromolecular medicine; vol. 14; pp. 112-118; Jun. 2012.
Calle et al.; U.S. Appl. No. 18/562,283 entitled "Neurostimulation parameter authentication and expiration system for nuerostimulation," filed Nov. 17, 2023.
Levine et al.; U.S. Appl. No. 18/431,974 entitled "Vagus nerve stimulation pre-screening test," filed Feb. 3, 2024.
Li et al.; U.S. Appl. No. 18/645,129 entitled "System and methods of stimulation at trigeminaly innervated regions for disorders of cerebral perfusion," filed Apr. 24, 2024.
Levine et al.; U.S. Appl. No. 18/730,753 entitled "Treatment of inflammatory disorders," filed Jul. 19, 2024.
Hebb et al.; Creating the Feedback Loop: Closed-Loop Neurostimulation; Neurosurgery Clinics of North America; 25(1); pp. 187-204; Jan. 28, 2014.
McLean et al.; Delayed nerve stimulation promotes axon-protective neurofilament phosphorylation, accelerates immune cell clearance and enhances remyelination in vivo in focally demyelinated nerves; PloS one; 9(10); e110174; 17 pages; Oct. 13, 2014.

* cited by examiner

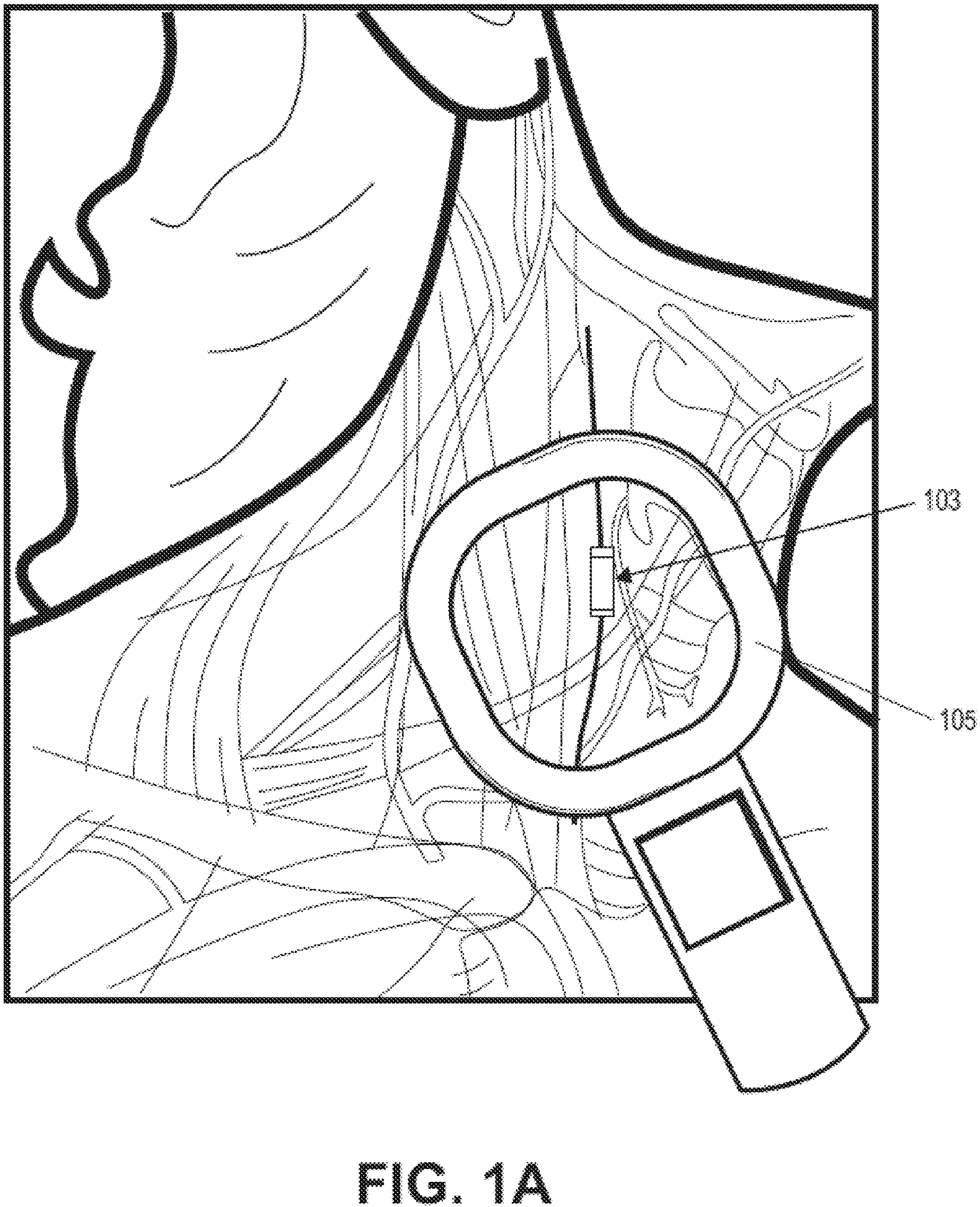


FIG. 1A

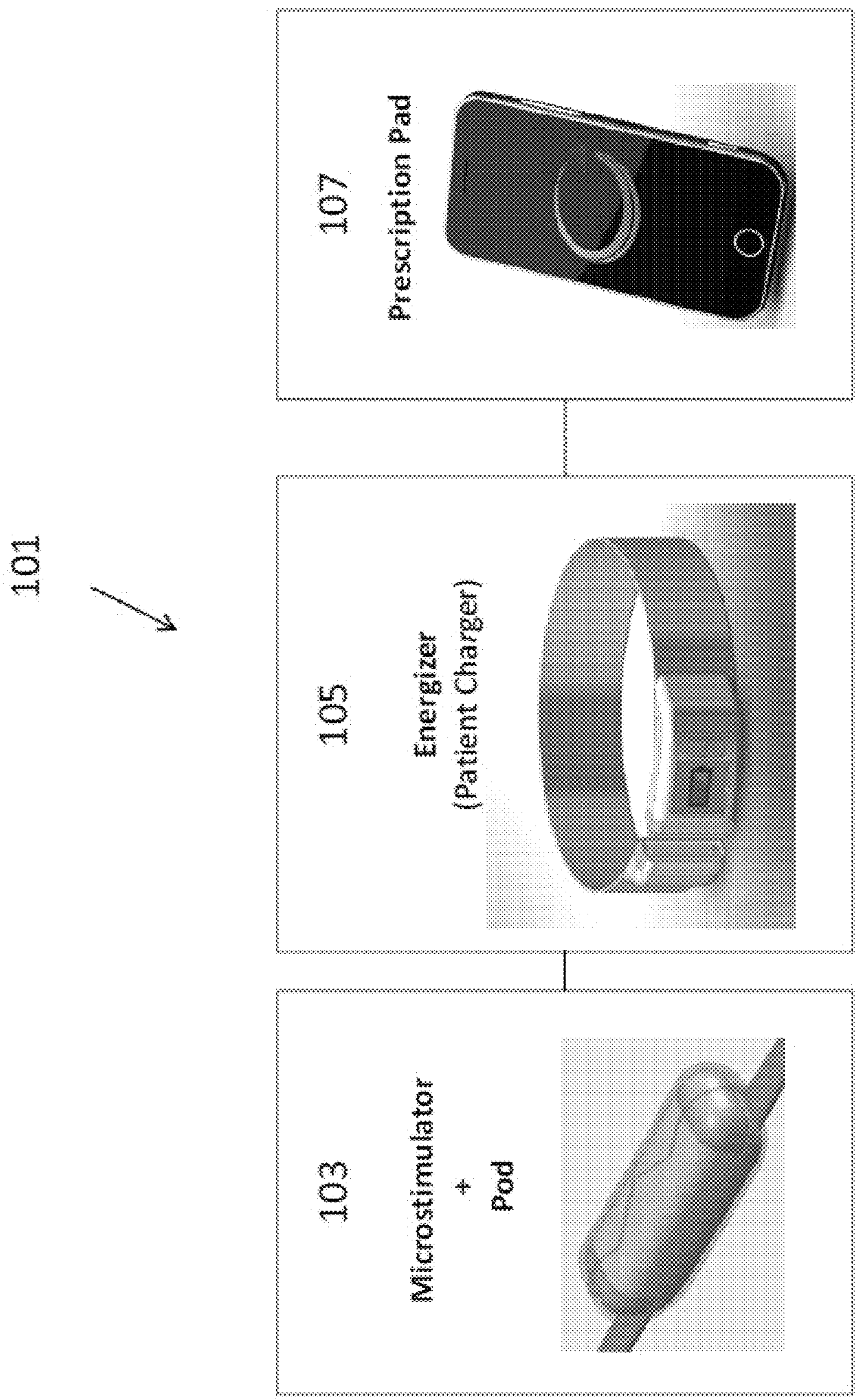

101
103
Microstimulator
+
Pod
105
Energizer
(Patient Charger)
107
Prescription Pad

FIG. 1B

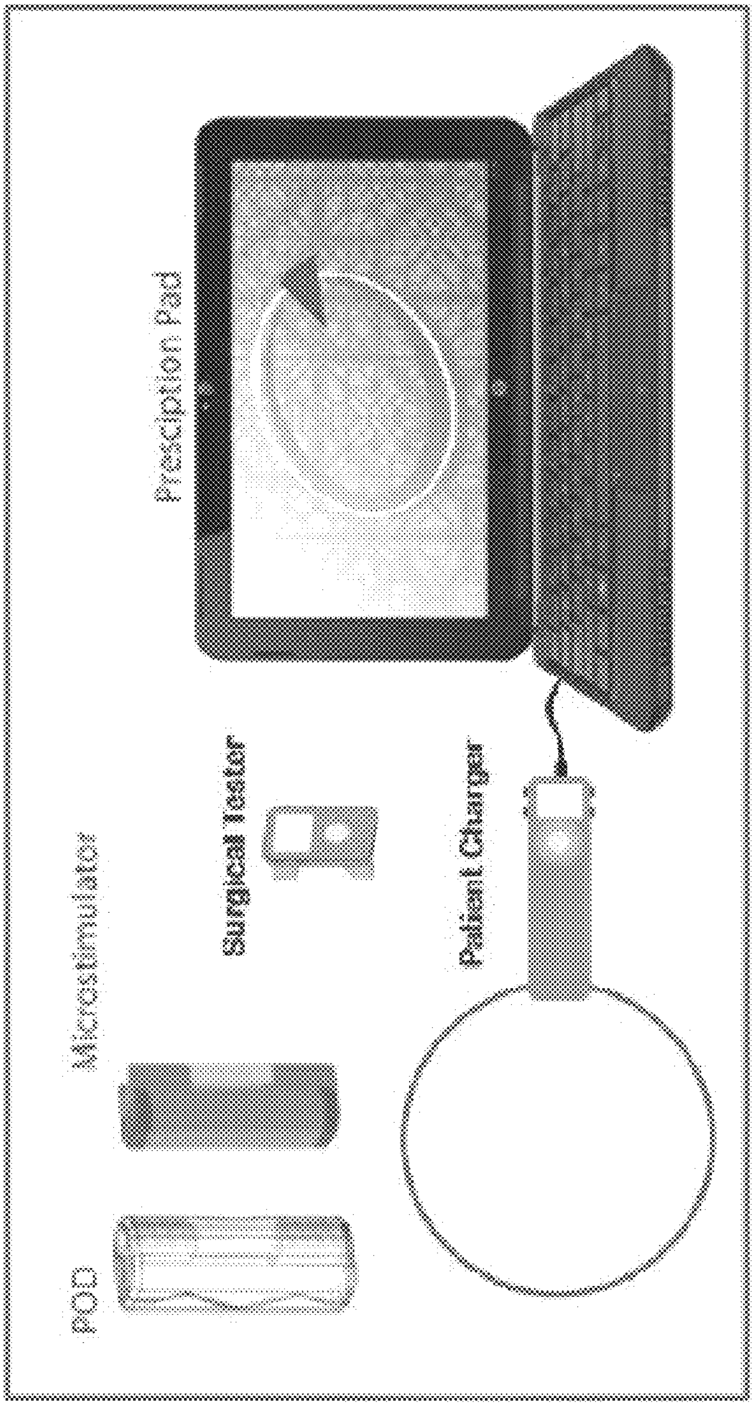
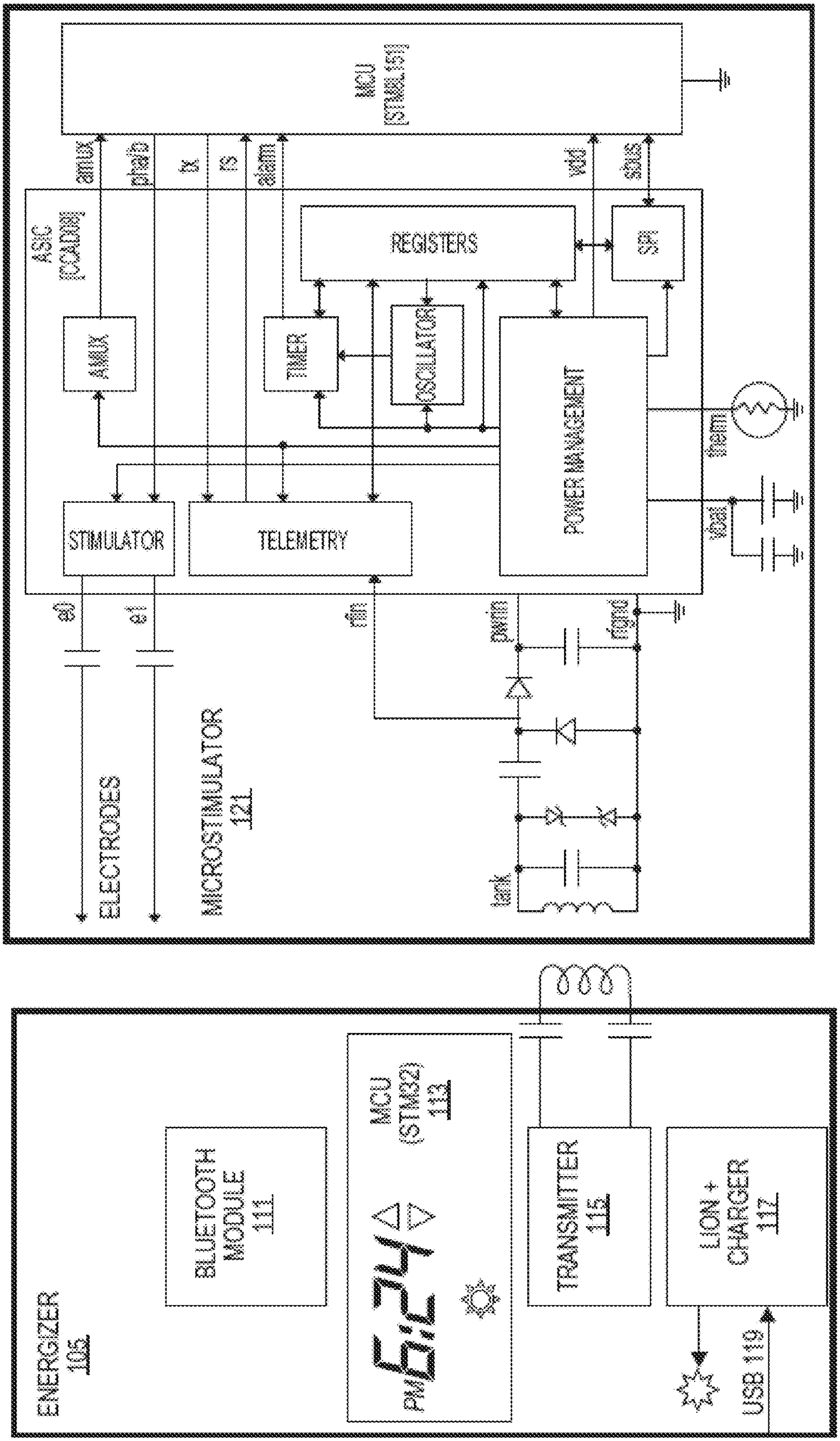

Presciption Pad
Surgical Tester
Patient Charger
Microstimulator
POD

FIG. 1C

FIG. 1D


MCU
ASC
amux
pha/b
tx
rs
alarm
vdd
sbus
REGISTERS
SPI
AMUX
TIMER
OSCILLATOR
POWER MANAGEMENT
STIMULATOR
TELEMETRY
therm
vbat
e0
e1
rfin
pwrin
rfgnd
tank
ELECTRODES
MICROSTIMULATOR
121
ENERGIZER
105
BLUETOOTH MODULE
111
MCU
(STM32)
113
PM 6:24
TRANSMITTER
115
LION + CHARGER
117
USB 119

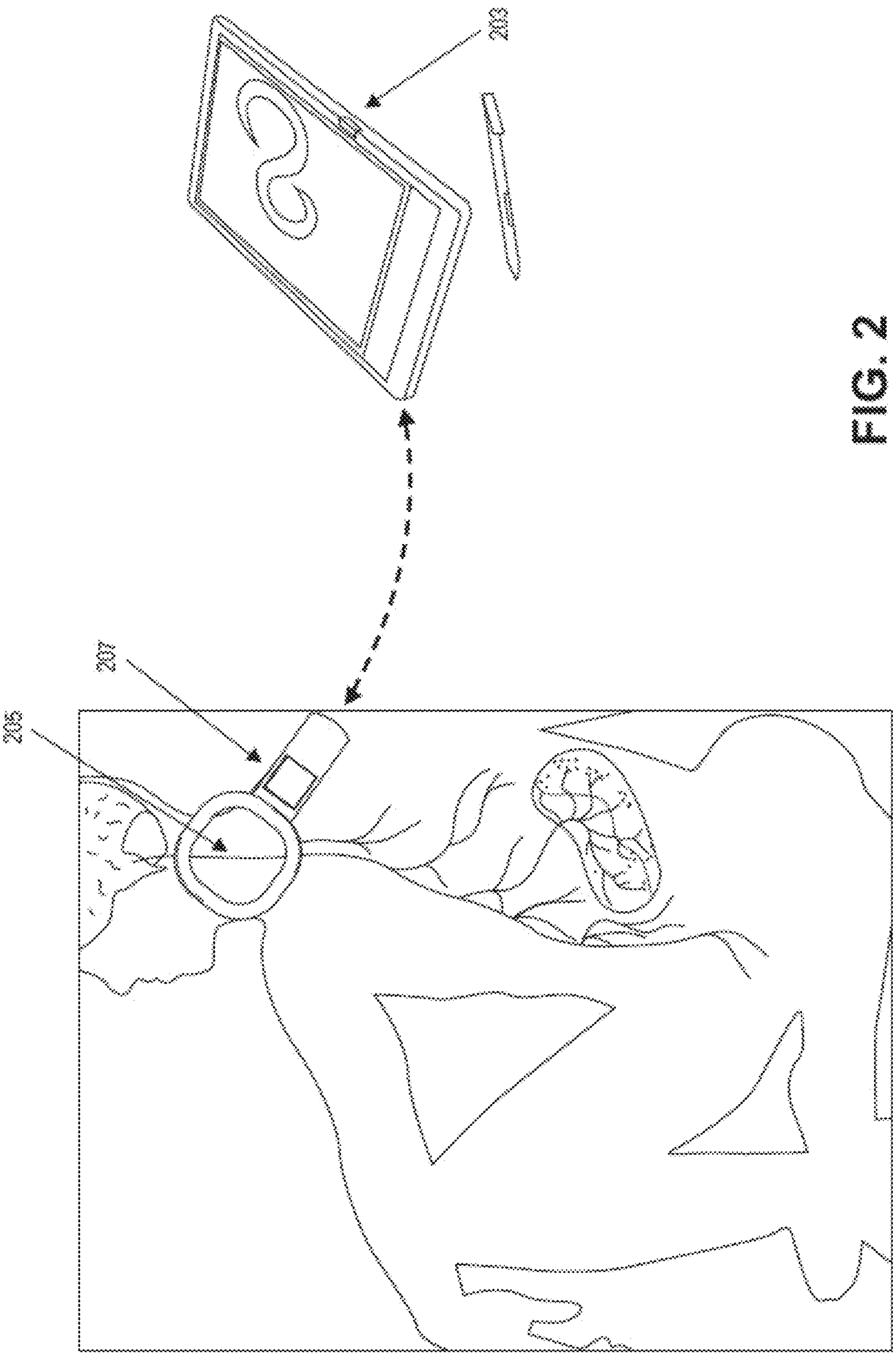


FIG. 2

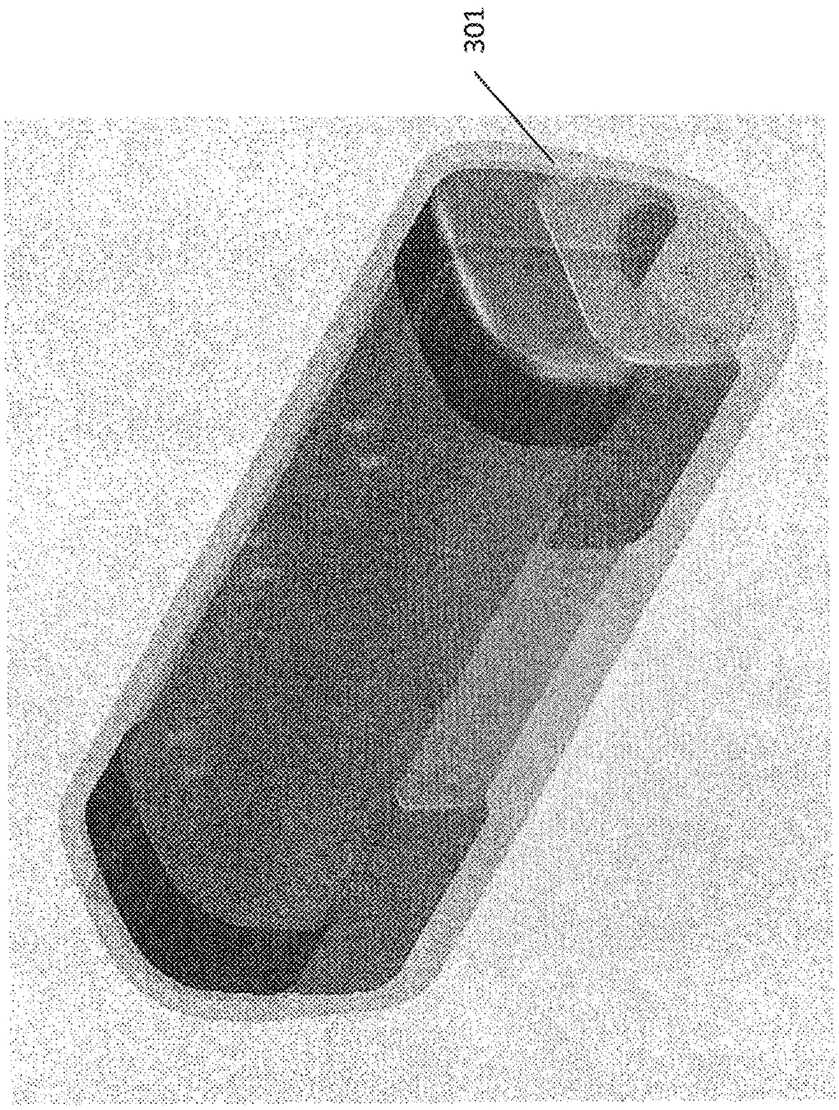


FIG. 3A

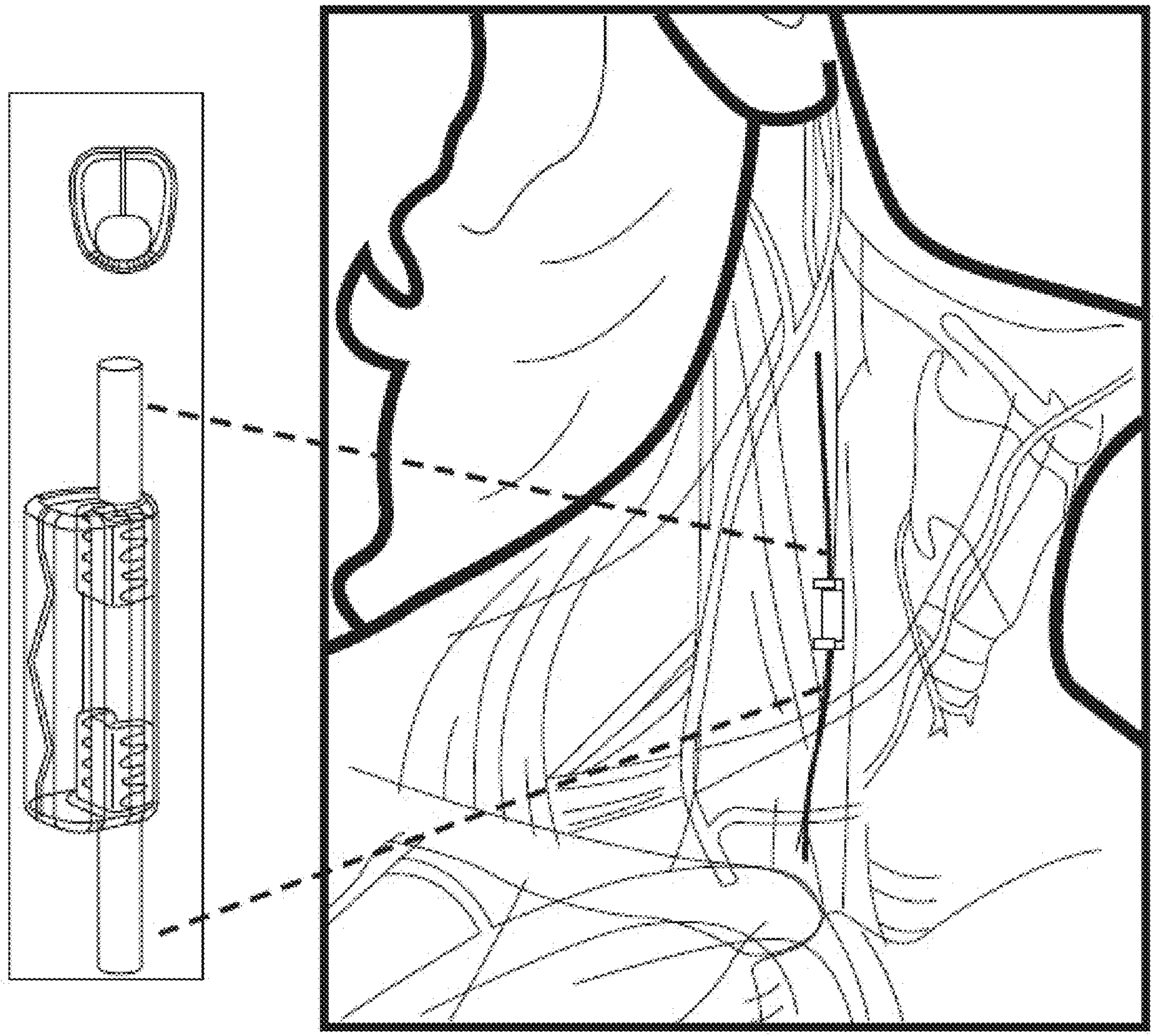


FIG. 3B

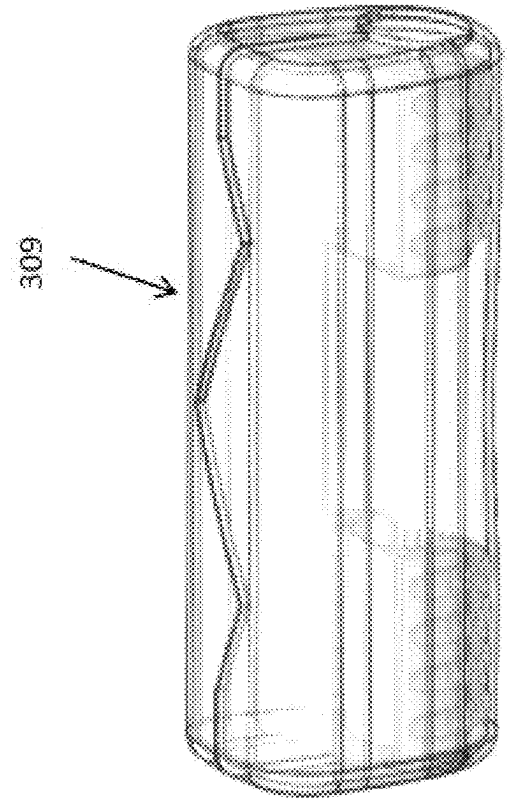


FIG. 3D

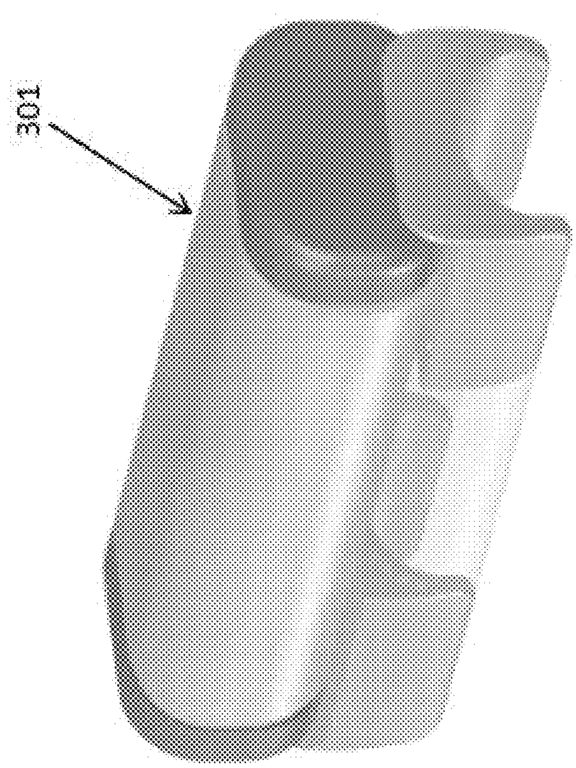


FIG. 3C

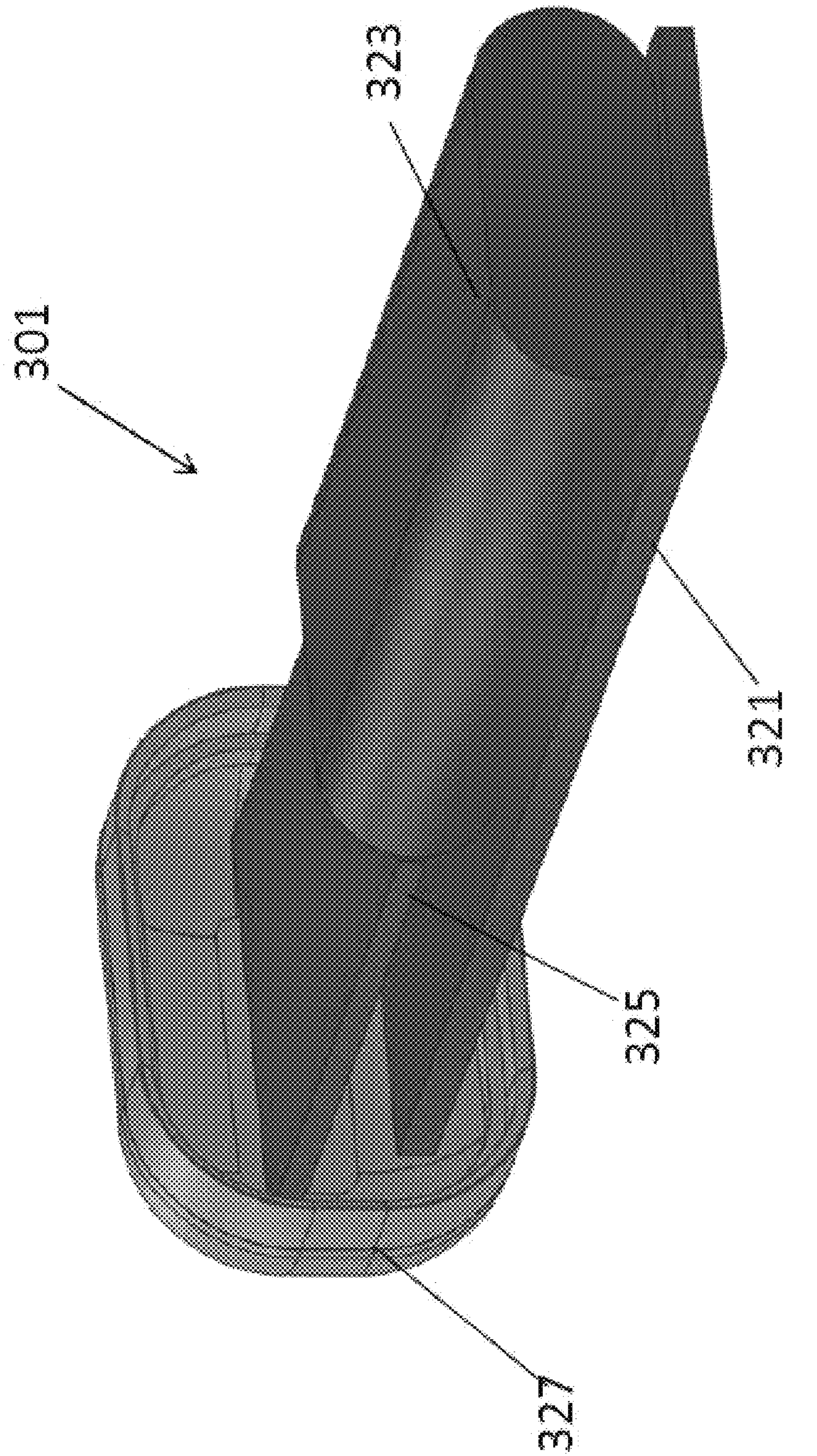


FIG. 3E

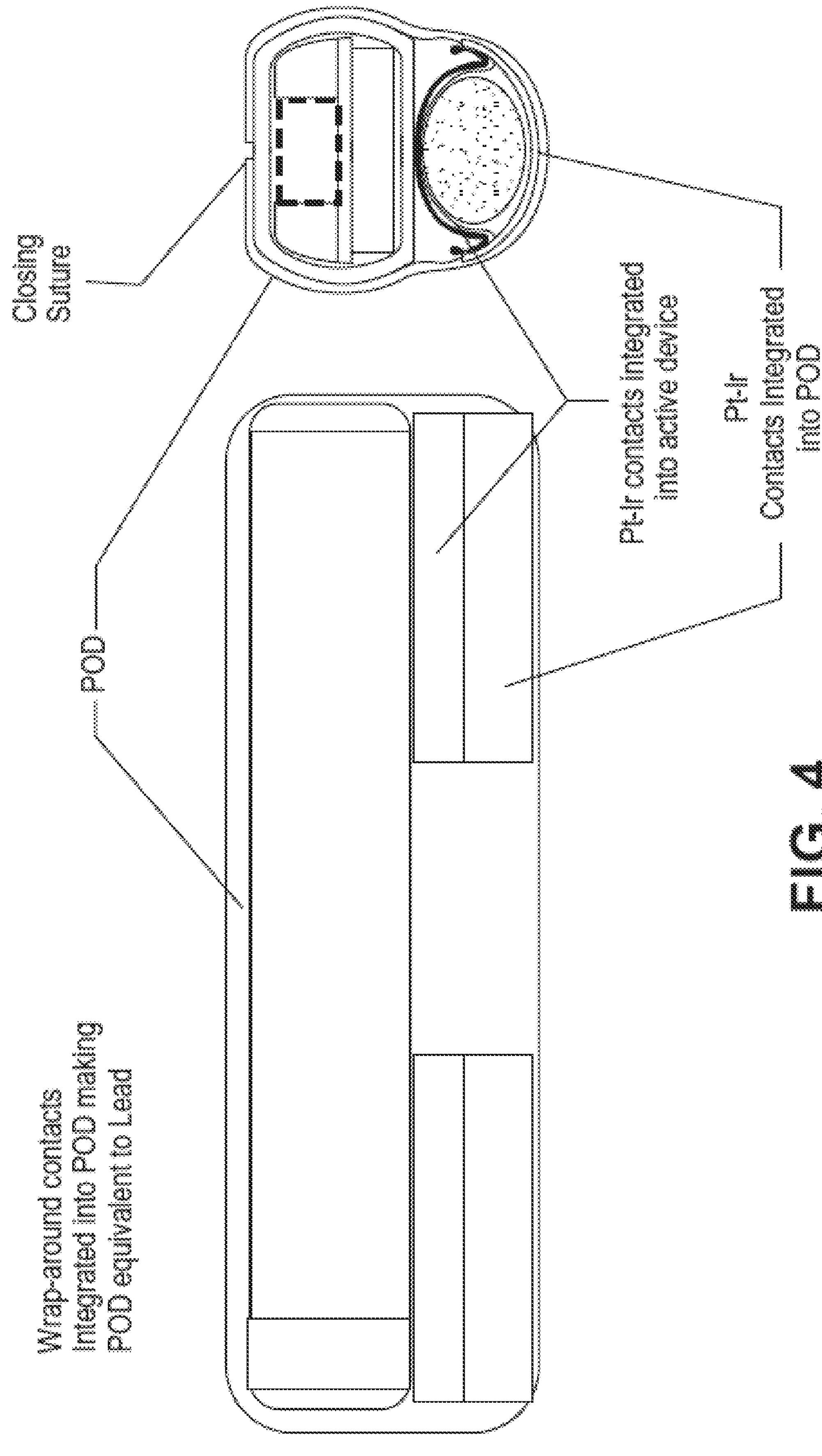

Closing Suture
POD
Pt-Ir contacts integrated into active device
Pt-Ir Contacts Integrated into POD
Wrap-around contacts Integrated into POD making POD equivalent to Lead

FIG. 4

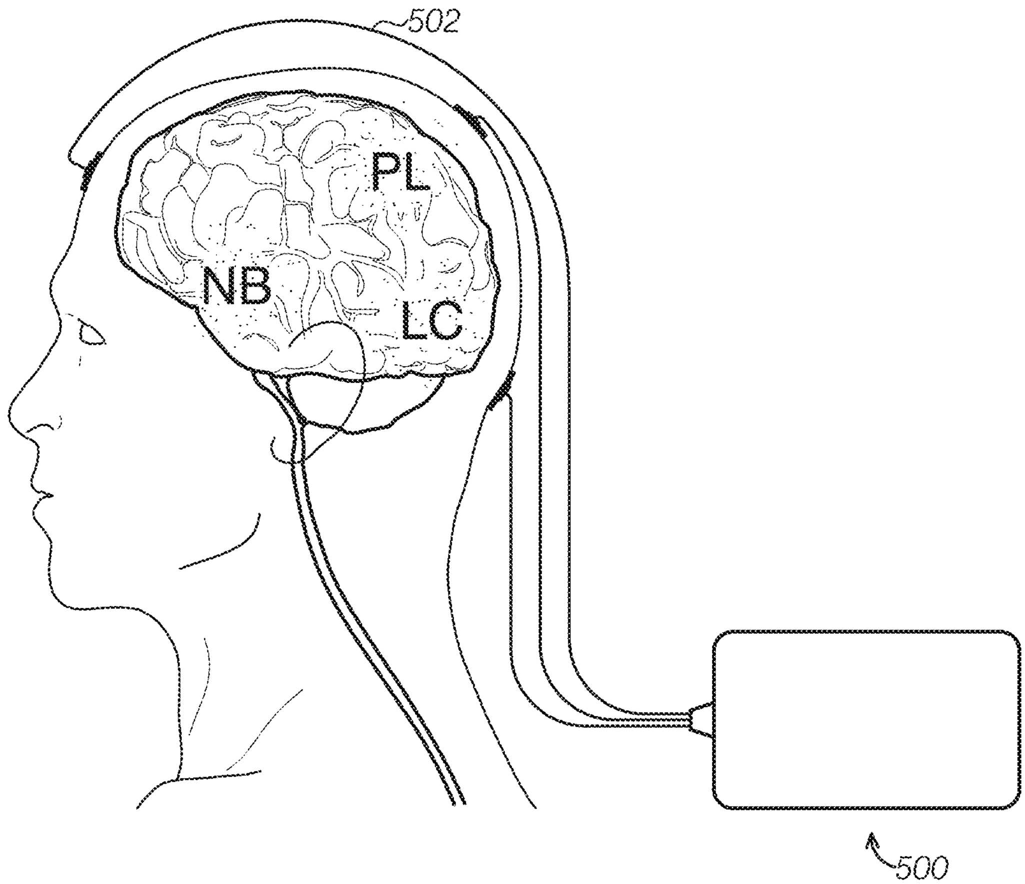


FIG.5

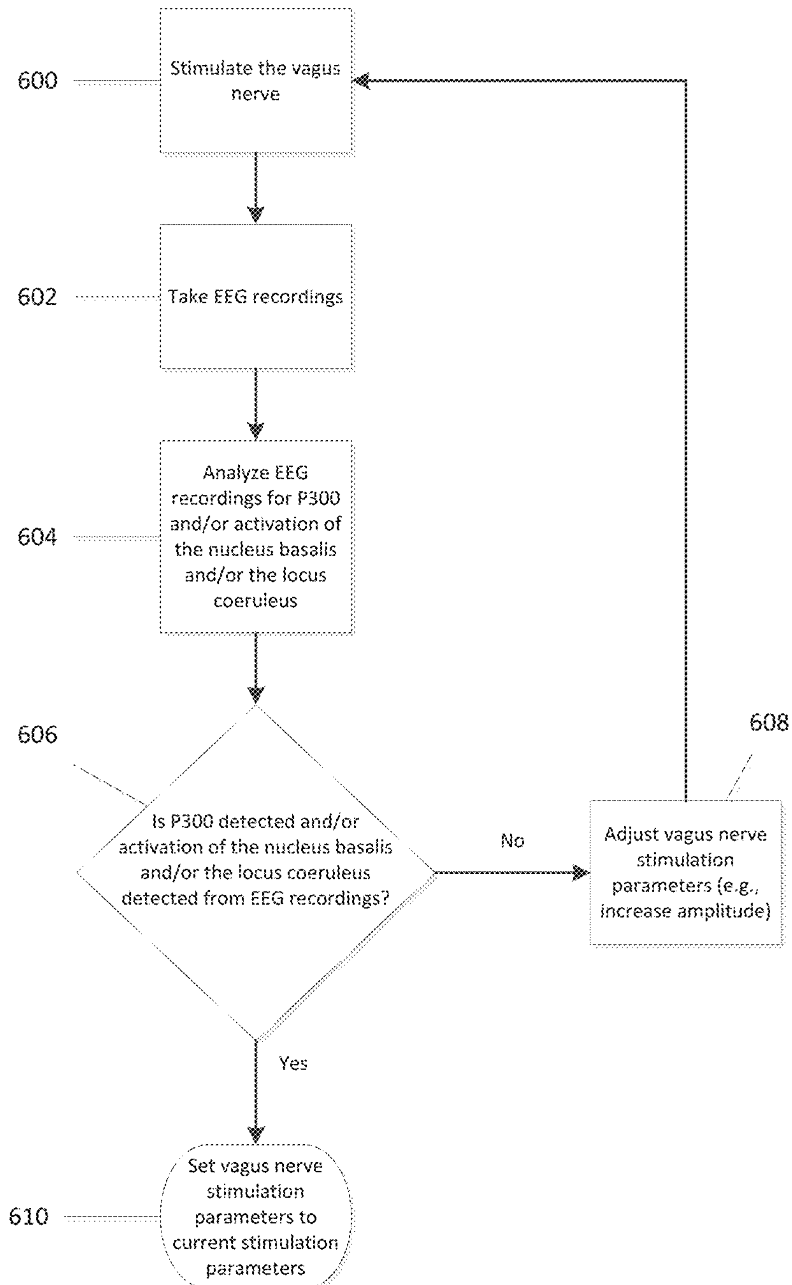

600
Stimulate the vagus nerve
602
Take EEG recordings
604
Analyze EEG recordings for P300 and/or activation of the nucleus basalis and/or the locus coeruleus
606
Is P300 detected and/or activation of the nucleus basalis and/or the locus coeruleus detected from EEG recordings?
No
608
Adjust vagus nerve stimulation parameters (e.g., increase amplitude)
Yes
610
Set vagus nerve stimulation parameters to current stimulation parameters

FIG. 6

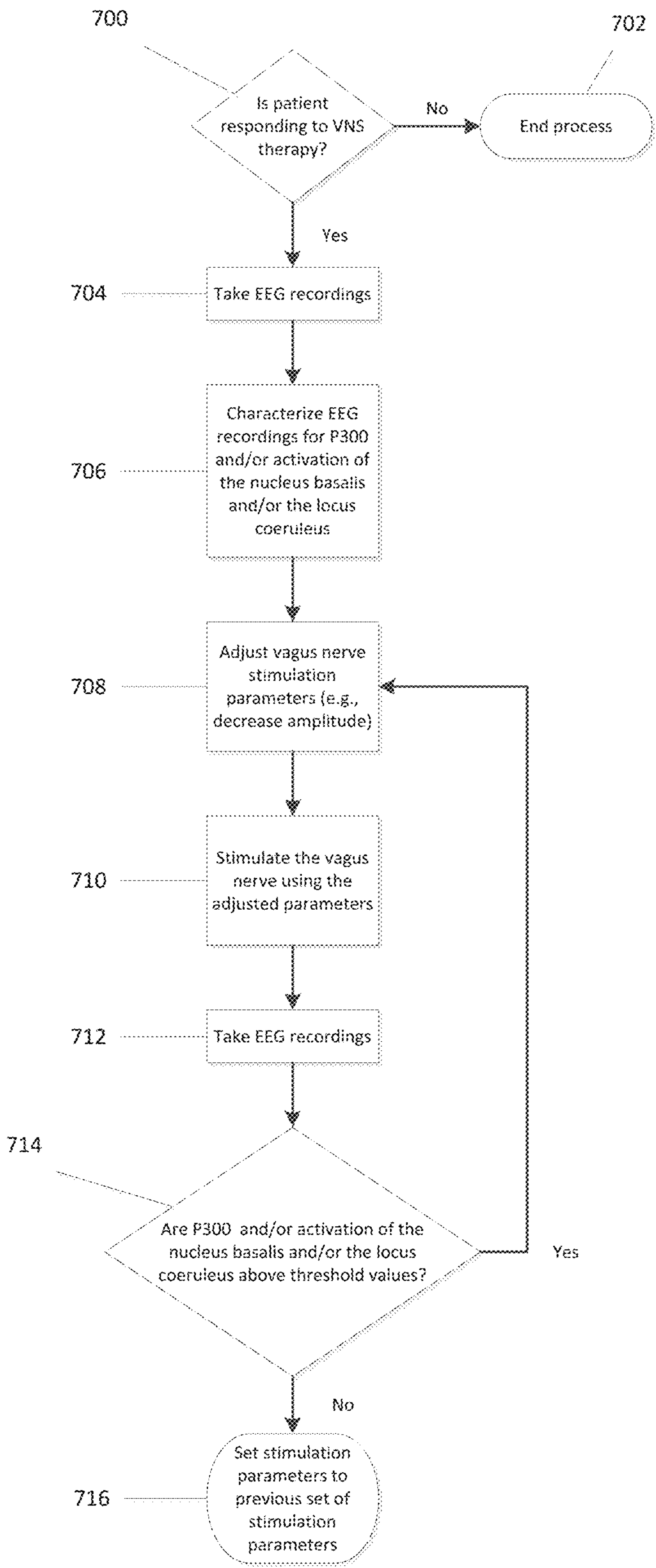

700
702
Is patient responding to VNS therapy?
No
End process
Yes
704
Take EEG recordings
706
Characterize EEG recordings for P300 and/or activation of the nucleus basalis and/or the locus coeruleus
708
Adjust vagus nerve stimulation parameters (e.g., decrease amplitude)
710
Stimulate the vagus nerve using the adjusted parameters
712
Take EEG recordings
714
Are P300 and/or activation of the nucleus basalis and/or the locus coeruleus above threshold values?
Yes
No
716
Set stimulation parameters to previous set of stimulation parameters

FIG. 7

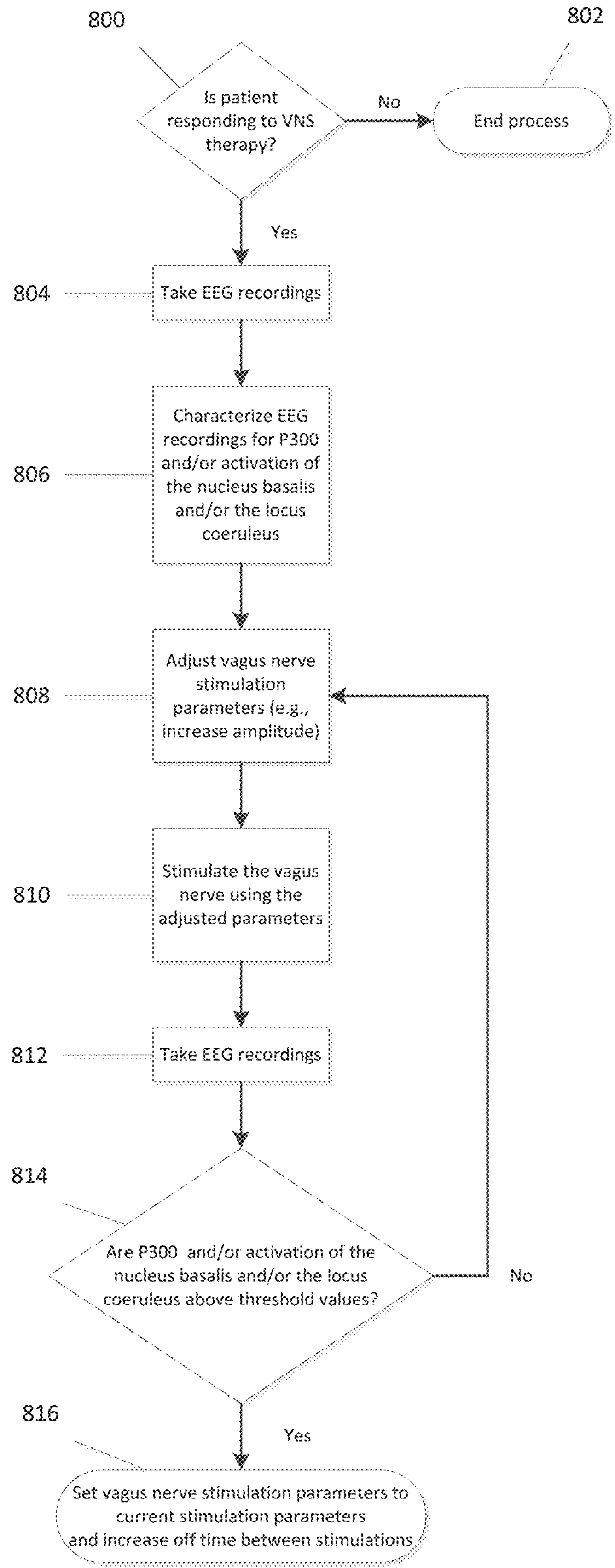

800
802
Is patient responding to VNS therapy?
No
End process
Yes
804
Take EEG recordings
806
Characterize EEG recordings for P300 and/or activation of the nucleus basalis and/or the locus coeruleus
808
Adjust vagus nerve stimulation parameters (e.g., increase amplitude)
810
Stimulate the vagus nerve using the adjusted parameters
812
Take EEG recordings
814
Are P300 and/or activation of the nucleus basalis and/or the locus coeruleus above threshold values?
No
816
Yes
Set vagus nerve stimulation parameters to current stimulation parameters and increase off time between stimulations

FIG. 8

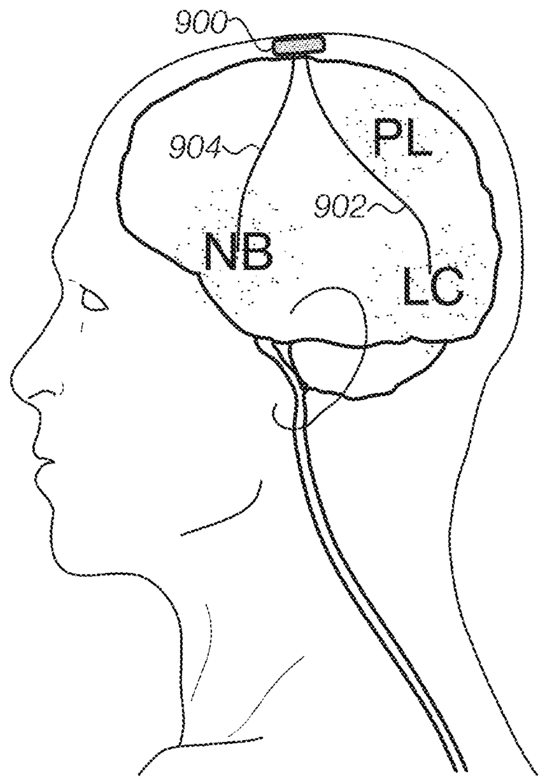


FIG.9

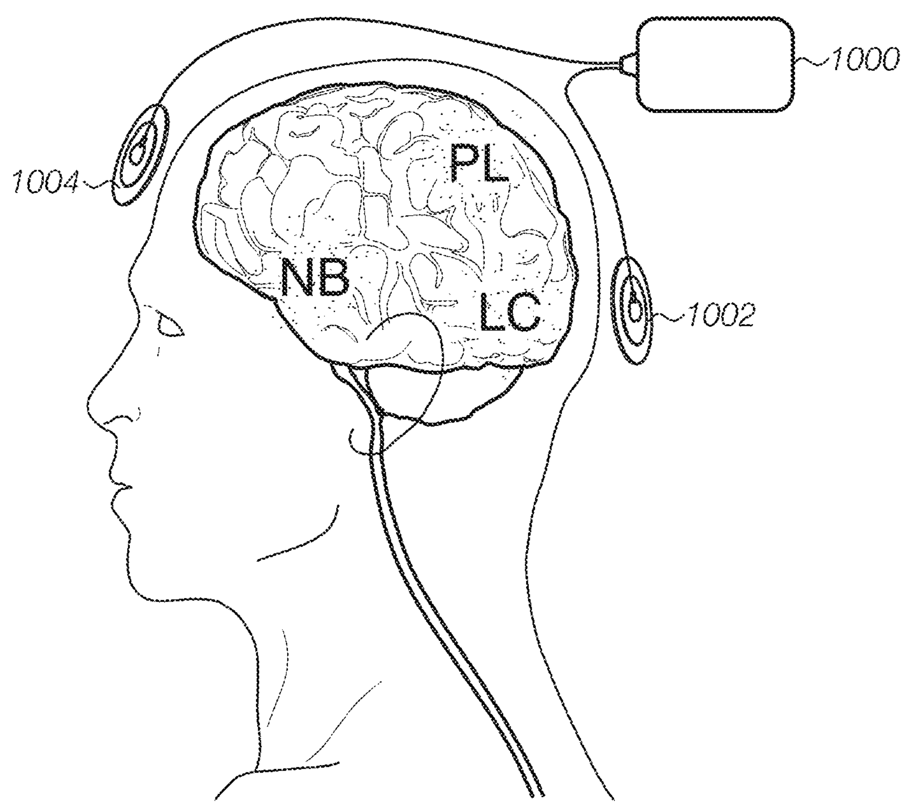


FIG.10

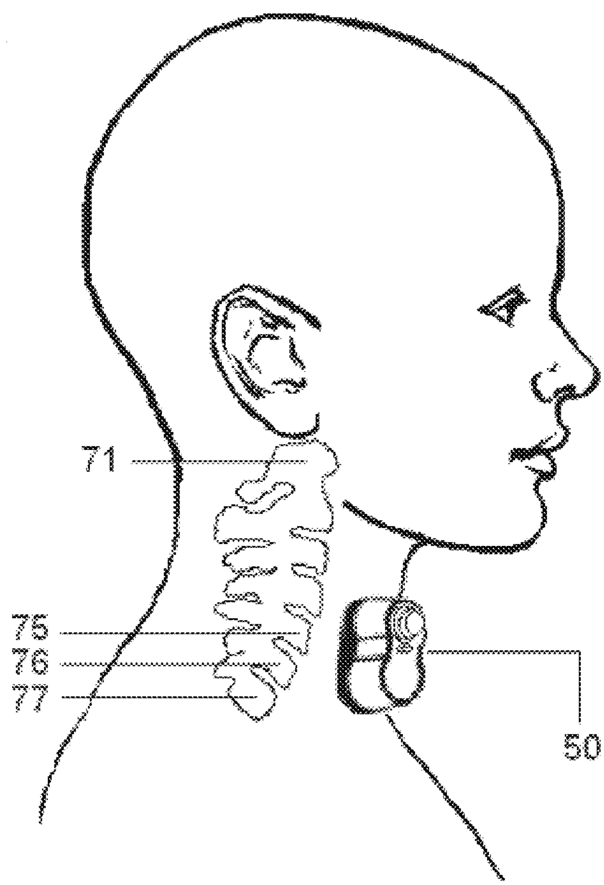


FIG. 11

SYSTEMS AND METHODS FOR STIMULATING AND/OR MONITORING LOCI IN THE BRAIN TO TREAT INFLAMMATION AND TO ENHANCE VAGUS NERVE STIMULATION

CROSS REFERENCE TO RELATED APPLICATIONS

This patent application is a divisional of U.S. patent application Ser. No. 14/922,022, titled "SYSTEMS AND METHODS FOR STIMULATING AND/OR MONITORING LOCI IN THE BRAIN TO TREAT INFLAMMATION AND TO ENHANCE VAGUS NERVE STIMULATION," filed Oct. 23, 2015, now U.S. Pat. No. 11,311,725, which claims priority to U.S. Provisional Patent Application No. 62/068,473, titled "EXTREMELY LOW DUTY-CYCLE ACTIVATION OF THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY, AND TRAINING THEREOF, TO TREAT CHRONIC INFLAMMATION," filed Oct. 24, 2014, which is herein incorporated by reference in its entirety.

Some variations of the methods and apparatuses described in this patent application may be related to the following U.S. patent applications: U.S. patent application Ser. No. 12/620,413, filed on Nov. 17, 2009 and titled, "DEVICES AND METHODS FOR OPTIMIZING ELECTRODE PLACEMENT FOR ANTI-INFLAMATORY STIMULATION" (US-2010-0125304); U.S. patent application Ser. No. 12/874,171, filed on Sep. 1, 2010 and titled, "PRESCRIPTION PAD FOR TREATMENT OF INFLAMMATORY DISORDERS" (US-2011-0054569); U.S. patent application Ser. No. 12/917,197, filed on Nov. 1, 2010 and titled, "MODULATION OF THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY TO TREAT PAIN OR ADDICTION" (US-2011-0106208); U.S. patent application Ser. No. 12/978,250, filed on Dec. 23, 2010 and titled, "NEURAL STIMULATION DEVICES AND SYSTEMS FOR TREATMENT OF CHRONIC INFLAMMATION" (US-2011-0190849); U.S. patent application Ser. No. 12/797,452, filed on Jun. 9, 2010 and titled, "NERVE CUFF WITH POCKET FOR LEADLESS STIMULATOR" (US-2010-0312320); U.S. patent application Ser. No. 13/467,928, filed on May 9, 2012 and titled, "SINGLE-PULSE ACTIVATION OF THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY TO TREAT CHRONIC INFLAMMATION" (US-2012-0290035); and U.S. patent application Ser. No. 13/338,185, filed on Dec. 27, 2011 and titled, "MODULATION OF SIRTUINS BY VAGUS NERVE STIMULATION." Each of these patent applications is herein incorporated by reference in its entirety.

Some variations of the methods and apparatuses described in this patent application may be related to the following PCT application: International Application No. PCT/US2014/033690, filed Apr. 10, 2014, which is herein incorporated by reference in its entirety.

INCORPORATION BY REFERENCE

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

For example, the following reference are incorporated by reference herein in their entireties:

1. Cheyuo, C., et al., The parasympathetic nervous system in the quest for stroke therapeutics. J Cereb Blood Flow Metab, 2011. 31(5): p. 1187-95.
2. Engineer, N. D., A. R. Moller, and M. P. Kilgard, Directing neural plasticity to understand and treat tinnitus. Hear Res, 2013. 295: p. 58-66.
3. Groves, D. A., E. M. Bowman, and V. J. Brown, Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. Neuroscience Letters, 2005. 379(3): p. 174-179.
4. Don, A. E. and G. Debonnel, Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. J Pharmacol Exp Ther, 2006. 318(2): p. 890-8.
5. Clark, K. B., et al., Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat Neurosci, 1999. 2(1): p. 94-8.
6. Engineer, N. D., et al., Reversing pathological neural activity using targeted plasticity. Nature, 2011. 470 (7332): p. 101-4.
7. Diamond, B. and K. J. Tracey, Mapping the immunological homunculus. Proc Natl Acad Sci USA, 2011. 108(9): p. 3461-2.
8. Swick, D., et al., Locus coeruleus neuronal activity in awake monkeys: relationship to auditory P300-like potentials and spontaneous EEG. Experimental Brain Research, 1994. 101(1): p. 86-92.
9. Neuhaus, A. H., et al., P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder. J Affect Disord, 2007. 100(1-3): p. 123-8.

FIELD

Embodiments of the invention relate generally to neuromodulation of the vagus nerve for the treatment of inflammation, and more specifically to neuromodulation of the vagus nerve involving feedback and/or stimulation from the central nervous system.

BACKGROUND

Some neuromodulation devices have the ability to modulate their own stimulation settings quickly based on immediate feedback from target tissue (e.g. muscle) that they are stimulating, since the target tissue responds quickly to stimulation. For example, electromyography (EMG) can be used to record and evaluate the electrical activity of muscles, which provides information regarding the activation level and/or recruitment of the muscles. This information can be processed and used to modulate the neurostimulation parameters applied to the muscles, thereby improving the efficacy of the stimulation device.

Vagus nerve stimulation (VNS) for the treatment of chronic inflammatory diseases, on the other hand, is not easily programmed for optimal result, as decreases in inflammation take hours to days to manifest. Consequently, it would be desirable to identify alternative markers or surrogates that indicate activation of the cholinergic anti-inflammatory pathway by VNS. In addition, it would be desirable to use these alternative markers or surrogates to identify patients that may be suitable for receiving VNS therapy. Furthermore, it would be desirable to directly modulate these markers or surrogates as an alternative or supplemental way to treat inflammation.

SUMMARY OF THE DISCLOSURE

The present invention relates generally to neuromodulation of the vagus nerve for the treatment of inflammation, and more specifically to neuromodulation of the vagus nerve involving feedback and/or stimulation from the central nervous system.

In some embodiments, a method for inducing long term potentiation of the inflammatory reflex in a patient is provided. The method can include stimulating the vagus nerve of the patient according to a set of stimulation parameters; recording an EEG after the step of stimulating the vagus nerve; determining from the recorded EEG whether at least one of the nucleus basalis and the locus coeruleus has been activated by the vagus nerve stimulation; and adjusting the set of stimulation parameters based on the determination from the recorded EEG whether at least one of the nucleus basalis and the locus coeruleus has been activated.

In some embodiments, the step of adjusting the set of stimulation parameters includes increasing a stimulation amplitude.

In some embodiments, the method further includes recording a baseline EEG.

In some embodiments, the step of determining from the recorded EEG whether at least one of the nucleus basalis and the locus coeruleus has been activated by the vagus nerve stimulation comprises comparing the recorded EEG with the baseline EEG.

In some embodiments, a method for inducing long term potentiation of the inflammatory reflex in a patient is provided. The method can include stimulating the vagus nerve according to a set of stimulation parameters sufficient for activating at least one of the nucleus basalis and the locus coeruleus.

In some embodiments, the set of stimulation parameters includes an amplitude between about 0.1 and 3 mA, a frequency between about 1 Hz and 30 Hz, a pulse width between about 100 uS and 500 uS, and a duration between about 0.5 second to 10 minutes.

In some embodiments, a method for prescreening a patient is provided. The method can include noninvasively stimulating the vagus nerve; recording an EEG; and determining whether the patient will be responsive to an invasive vagus nerve stimulation based on an analysis of the EEG.

In some embodiments, the step of determining whether the patient will be responsive to an invasive vagus nerve stimulation based on an analysis of the EEG includes determining whether P300 is present in the EEG.

In some embodiments, the step of determining whether the patient will be responsive to an invasive vagus nerve stimulation based on an analysis of the EEG includes determining with the EEG whether at least one of the nucleus basalis and the locus coeruleus was activated by the noninvasive vagus nerve stimulation.

In some embodiments, the step of noninvasively stimulating the vagus nerve includes noninvasively stimulating the auricular branch of the vagus nerve.

In some embodiments, the noninvasive stimulation of the auricular branch of the vagus nerve is electrical.

In some embodiments, the noninvasive stimulation of the auricular branch of the vagus nerve is mechanical.

In some embodiments, the step of recording the ECG takes place after the step of noninvasively stimulating the vagus nerve.

In some embodiments, the step of recording the ECG takes place during the step of noninvasively stimulating the vagus nerve.

In some embodiments, a method for providing feedback control during vagus nerve stimulation of a patient is provided. The method can include stimulating the vagus nerve with a vagus nerve stimulator; recording an EEG to detect at least one of P300, activation of the nucleus basilis, and activation of the locus coeruleus; and adjusting an amplitude of the stimulation to the vagus nerve until at least one of P300, activation of the nucleus basilis, and activation of the locus coeruleus is detected in the EEG.

In some embodiments, the method further includes programming the vagus nerve stimulator with a set of stimulation parameters based on the step of adjusting the amplitude of the stimulation to the vagus nerve until at least one of P300, activation of the nucleus basilis, and activation of the locus coeruleus is detected in the EEG.

In some embodiments, the step of adjusting the amplitude includes increasing the amplitude when the patient is not responding to the stimulation of the vagus nerve.

In some embodiments, the step of adjusting the amplitude includes decreasing the amplitude when the patient is responding well to the stimulation of the vagus nerve.

In some embodiments, the method further includes increasing a stimulation interval after the step of adjusting the amplitude of the stimulation to the vagus nerve until at least one of P300, activation of the nucleus basilis, and activation of the locus coeruleus is detected in the EEG.

In some embodiments, a system for stimulating a nerve of a patient is provided. The system can include an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of programmed stimulation parameters; an EEG recording device configured to record an EEG of the patient; and a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG, and adjust the set of programmed stimulation parameters based on the determination of whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG.

In some embodiments, the controller is located in a prescription pad.

In some embodiments, the controller is located in an energizer configured to provide power to the implantable nerve stimulator.

In some embodiments, the controller is located in the EEG recording device.

In some embodiments, the set of programmed stimulation parameters includes a pulse amplitude, a pulse width, and a pulse frequency.

In some embodiments, a method for treating a patient suffering from inflammation is provided. The method can include stimulating at least one of the nucleus basalis and the locus coeruleus with an electrode implanted within the patient's brain; and reducing a level of inflammation in the patient.

In some embodiments, the step of stimulating at least one of the nucleus basalis and the locus coeruleus with an electrode implanted within the patient's brain includes delivering an electrical stimulus having a current between 10 to 100 uA, a frequency of 1 to 500 Hz, and a duration of up to 120 minutes.

In some embodiments, a method for treating a patient suffering from inflammation is provided. The method can include stimulating at least one of the nucleus basalis and the locus coeruleus with a focused magnetic field; and reducing a level of inflammation in the patient.

In some embodiments, the step of stimulating at least one of the nucleus basalis and locus coeruleus with the focused magnetic field includes generating the focused magnetic field with a transcranial magnetic coil.

In some embodiments, the step of stimulating at least one of the nucleus basalis and locus coeruleus with the focused magnetic field includes generating the magnetic field with a frequency below 3 Hz, a field strength below 3 Tesla, and a duration between 5 to 60 minutes.

In some embodiments, the step of stimulating at least one of the nucleus basalis and locus coeruleus with the focused magnetic field includes generating the magnetic field with a frequency between 3 to 25 Hz, a field strength below 3 Tesla, and a duration between 5 to 60 minutes.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the claims that follow. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. **1**A shows one variation of a system for modulating chronic inflammation including a leadless microstimulator (shown connected to the vagus nerve) and an external charger/controller.

FIG. **1**B shows another variation of a system for modulating chronic inflammation, including a microstimulator, charger ("energizer"), and system programmer/controller ("prescription pad").

FIG. **1**C shows another variations of a system for modulating chronic inflammation, including a microstimulator, a securing device (POD) for securing the leadless stimulator to the nerve, an external charger, a system programmer/controller ("prescription pad") and an optional surgical tester.

FIG. **1**D is a block diagram schematically illustrating the microstimulator and the charger.

FIG. **2** illustrates one variation of an external system programmer/controller wirelessly connected to a microstimulator.

FIG. **3**A shows one variation of a microstimulator in a POD configured to surround a nerve of the inflammatory reflex. FIG. **3**B shows an enlarged view of the microstimulator and POD. FIG. **3**C shows another variation of a microstimulator; FIG. **3**D shows the microstimulator of FIG. **3**C within a POD. FIG. **3**E shows another variation of the microstimulator.

FIG. **4** shows a schematic diagram of a microstimulator and POD around vagus nerve.

FIG. **5** illustrates an embodiment of an EEG recording system for detecting P300 and/or activation of the locus coeruleus and/or nucleus basalis.

FIG. **6** illustrates a flow chart that describes a method for modulating vagus nerve stimulation using feedback from EEG recordings.

FIG. **7** illustrates a flow chart that describes another method for modulating vagus nerve stimulation using feedback from EEG recordings.

FIG. **8** illustrates a flow chart that describes yet another method for modulating vagus nerve stimulation using feedback from EEG recordings.

FIG. **9** illustrates an embodiment of a deep brain stimulator with electrodes positioned at the nucleus basalis and locus coeruleus.

FIG. **10** illustrates an embodiment of a transcranial magnetic stimulator.

FIG. **11** illustrates an embodiment of a transcutaneous electrical nerve stimulator.

DETAILED DESCRIPTION

Various regions or neural groups in the brain and central nervous system are linked to the vagus nerve through sympathetic and/or efferent neural pathways. Consequently, activation or stimulation of these regions or neuronal groups may initiate and/or modulate vagus nerve activity. Alternatively, activation or stimulation of the vagus nerve may initiate and/or modulate activity in these various regions or neural groups. Because activation of the vagus nerve may result in activation of the these regions or neural groups, these regions or neural groups can be monitored as surrogates or proxies for determining whether the vagus nerve has been successfully activated by the VNS.

For example, the nucleus basalis (NB) is composed of a neural group in the substantia innominata of the basal forebrain, next to the hypothalamus, and is a source of much of the acetylcholine in the brain. The degradation of the NB has been shown to play a role in Parkinson's and Alzheimer's disease. The NB receives noradrenergic innervation from the locus coeruleus and has neural projections to the caudate nucleus, globus pallidus, thalamus, hippocampus, cerebral cortex, and the brainstem. NB activity drives efferent vagal output [**1**] and activation of the NB increases attention and cortical plasticity.

Another region, the locus coeruleus (LC), is composed of a neural group located in the pons within the brainstem and is the principle source of norepinephrine (NE) in the brain. The LC has neural inputs from the nucleus tractus solitaries (NTS), dorsal raphe nucleus and projects to the NTS, dorsal raphe nucleus, thalamus, hypothalamus, amygdala, cortex, and the nucleus basalis. Activation of LC increases attention and cortical plasticity. LC coordinates VNS input with sympathetic output.

VNS can be used to activate both NB [2] and LC [3]. VNS causes increased firing within LC that can last for days [4]. VNS enhances recognition memory in humans [5]. Paired VNS (30 Hz, 0.8 mA, 100 uS, 0.5S, 2.5 hr duration) with tonal training results in reduction of rat tinnitus for more than 24 h [6]. These data show an increase in auditory cortical plasticity in topographically mapped brain regions with synchronous activation of NB and LC by VNS with training.

P300 describes an event-related potential (ERP) component that occur at latencies of about 250-700 msec and can be quantified by EEG recording as a positive voltage deflection. LC activity correlates with P300, as P300 is enhanced when LC activity is enhanced, and LC lesion or inhibition decreases P300 in monkeys [8]. There is a correlation between P300 activation and VNS responders in depression [9].

Therefore, during and/or after VNS, electrical activity from the NB and/or LC, including the P300, can be measured with EEG in order to provide immediate feedback or feedback within seconds or minutes after stimulation, rather than obtaining feedback from reduction in inflammation levels, which may take hours or longer to manifest. In some variations simply detecting the P300 during VNS and/or afterwards is sufficient to provide feedback and/or information. Alternatively, in some variations, the P300 may be detected based on a criterion (e.g., at or above a threshold such as a reference amplitude) before indicating a positive reading (e.g., triggering feedback). If electrical activity and/or the P300 is not detected or does not meet threshold values, the stimulation parameters, such as amplitude, can be adjusted until the electrical activity and/or P300 is detected and meets the threshold values that indicate NB and/or LC activation. It may not be necessary to provide a stimulus other than the VNS to elicit NB or LC activity; for example, any of the methods or apparatuses (systems and devices) described herein may examine the EEG during and/or just after the VNS.

Since P300 is an ERP, a predetermined stimulus can be provided to the patient to elicit P300. In some embodiments, the stimulus is the VNS itself. In other embodiments, the patient can be given a specific sensory, cognitive, or motor stimulus, and the EEG recording between about 250 msec and 700 msec after the stimulus can be analyzed for a positive voltage deflection that represents P300. Examples of a stimulus include an auditory stimulus provided using an auditory oddball paradigm and/or a visual stimulus provided using a visual oddball paradigm. The oddball paradigm presents a series of repetitive audio and/or visual stimuli that are interrupted by a deviant target stimulus, which the patient is asked to detect. Any of these stimuli can also be used to elicit electrical activity from the NB and/or LC.

Vagus Nerve Stimulation System

Systems for electrically stimulating one or more nerves to treat chronic inflammation may include an implantable, wireless microstimulator such as those described herein and an external charging device (which may be referred to as a charging wand, charger, or energizer). In some variations the system also includes a controller such as a "prescription pad" that helps control and regulate the dose delivered by the system. The microstimulator may be secured in position using a securing device (which may be referred to as a "POD") to hold the microstimulator in position around or adjacent to a nerve. These microstimulators are designed and adapted for treatment of chronic inflammation, and may be configured specifically for such use. Thus, an implantable microstimulator may be small, and adapted for the low duty-cycle stimulation to modulate inflammation. For example, the implantable microstimulator may hold a relatively small amount of power over weeks or even months and discharge it at a rate sufficient to modulate the anti-inflammatory pathway without significantly depressing heart rate or triggering any number of unwanted effects from the vagus nerve or other neural connections. Any of the nerves of the inflammatory reflex, including the vagus nerve, may be treated as described herein using the systems described.

For example, FIG. **1**A illustrates one variation of a system for treating chronic inflammation that includes a microstimulator contained in POD that is mounted on cervical vagus nerve and charged a programmed by an external charger/programmer unit. This variation of a system includes a microstimulator **103** that has been implanted to contact the vagus nerve as shown. The implant may be programmed, controlled and/or charged by a charger/controller **105** device. In this variation the charger/controller is a loop with a wand region.

FIG. **1**B shows another variation of a system for treating chronic inflammation that also includes an implantable microstimulator **103** (shown inserted into a POD to hold it in position relative to a nerve) and a charging device ("energizer" **105**) configured as a collar to be worn around the subject's neck and charge the implant. Optionally, the system may include a prescription pad **107** which may be a separate dedicated device or part of a mobile or other handheld device (e.g., an application to run on a handheld device).

FIG. **1**C shows another variation of a system for treating chronic inflammation. The systems described herein may also be referred to as systems for the neural stimulation of the cholinergic anti-inflammatory pathway (NCAP). These systems may be configured as chronic implantable systems. In some variations, the systems are configured to treat acutely (e.g., acute may 8 hours or less), sub-acutely (expected to occur for fewer than 30 days), or chronically (expected to occur for more than 30 days).

In general, the systems described herein may be configured to apply electrical stimulation at a minimum level necessary to modulate the inflammatory reflex (e.g., modulating cytokine release) characterized by the Chronaxie and rheobase. Chronaxie typically refers to the minimum time over which an electric current double the strength of the rheobase needs to be applied in order to stimulate the neuron. Rheobase is the minimal electrical current of infinite duration that results in an action potential. As used herein, cytokines refer to a category of signaling proteins and glycoproteins that, like hormones and neurotransmitters, are used extensively in cellular communication.

The NCAP Systems described herein are typically intended for the treatment of chronic inflammation through the use of implanted neural stimulation devices (microstimulators) to affect the Neural Stimulation of the Cholinergic Anti-inflammatory Pathway (NCAP) as a potential therapeutic intervention for rheumatologic and other inflammation-mediated diseases and disorders. Neurostimulation of the Cholinergic Anti-inflammatory Pathway (NCAP) has been shown to modulate inflammation. Thus, the treatment and management of symptoms manifested from the onset of disease (e.g., inflammatory disease) is based upon the concept of modulating the Cholinergic Anti-inflammatory Pathway. The NCAP pathway normally maintains precise restraint of the circulating immune cells. As used herein, the CAP is a reflex that utilizes cholinergic nerve signals traveling via the Vagus nerve between the brain, chemoreceptors, and the reticuloendothelial system (e.g., spleen, liver). Local release of pro-inflammatory cytokines (e.g., tumor necrosis factor or TNF) from resident immune cells is inhibited by the efferent, or indirectly by afferent vagus nerve signals. NCAP causes important changes in the function and microenvironment of the spleen, liver and other reticuloendothelial organs. Leukocytes which circulate systemically become "educated" as they traverse the liver and spleen are thereby functionally down regulated by the affected environment of the reticuloendothelial system. This effect can potentially occur even in the absence of an inflammatory condition.

Under this model, remote inflammation is then dampened by down-regulated cytokine levels. Stimulation of the vagus nerve with a specific regiment of electrical pulses regulates production of pro-inflammatory cytokines. In-turn, the down regulation of these cytokines may reduce localized inflammation in joints and other organs of patients with autoimmune and inflammatory disorders.

The NCAP System includes a neurostimulator that may trigger the CAP by stimulating the cervical vagus nerve. The NCAP System issues a timed burst of current controlled pulses with sufficient amplitude to trigger the CAP at a particular interval. These two parameters, Dose Amplitude and Dose Interval, may be used by a clinician to adjust the device. For example, the clinician may set the Dose Amplitude by modifying the current level. The Dose Interval may be set by changing the duration between Doses (e.g. 12, 24, 48 hours).

In some variations, dose amplitude may be set to within the Therapy Window. The Therapy window is defined as the lower limit of current necessary to trigger the CAP, and the upper limit is the level at which the Patient feels uncomfortable. The lower limit is called the Threshold (T), and the uncomfortable level is called Upper Comfort Level (UCL).

Dose Amplitude thresholds are nonlinearly dependent upon Current (I), Pulse width (PW), Pulse Frequency (PF), and Burst Duration (BD). Amplitude is primarily set by charge (Q), that is Current (I)×Pulse width (PW). In neurostimulation applications current has the most linear relationship when determining thresholds and working within the therapy window. Therefore, the clinician may modify Dose Amplitude by modifying current. The other parameters are held to experimentally determined defaults. Pulse width is selected to be narrow enough to minimize muscle recruitment and wide enough to be well above the chronaxie of the targeted neurons. Stimulus duration and pulse frequency was determined experimentally in Preclinical work.

Dose Interval may be specific for particular diseases and the intensity of diseases experienced by a patient. Our initial research has indicated that the cervical portion of the vagus nerve may be an ideal anatomic location for delivery of stimulation. The nerve runs through the carotid sheath parallel to the internal jugular vein and carotid artery. At this location, excitation thresholds for the vagus are low, and the nerve is surgically accessible. We have not found any significant difference in biomarker modulation (e.g., modulation of cytokines) between right and left. Even though the right vagus is thought to have lower thresholds than the left in triggering cardiac dysrythmias, the thresholds necessary for NCAP are much lower than those expected to cause such dysrythmias. Therefore a device delivering NCAP can safely be applied to either the right or left vagus.

We have also found, surprisingly, that the Therapy Window is maximized on the cervical vagus through the use of a bipolar cuff electrode design. Key parameters of the cuff may be: spacing and shielding of the contacts. For example, the contact points or bands may be spaced 1-2 diameters of the vagus nerve apart, and it may be helpful to shield current from these contacts from other nearby structures susceptible to inadvertent triggering. The cuff may be further optimized by using bands which are as long and wide as possible to reduce neurostimulator power requirements.

Thus, any variations of the systems described herein (e.g., the NCAP system) may be implemented with a Cuff, Lead and Implantable Pulse Generation (IPG), or a Leadless Cuff. The preferred implementation is a leadless cuff implemented by a microstimulator with integral electrode contacts in intimate contact with the nerve and contained within a Protection and Orientation Device (POD). This is illustrated in FIGS. **3**A and **3**B. The POD **301** may form a current shield, hold the microstimulator into place against the vagus nerve, and extend the microstimulator integral contacts with integral contacts in the POD itself. The POD is typically a polymer shell that encapsulates a microstimulator implant and that allows a nerve to run through the interior against the shell wall parallel to the length of the microstimulator implant. Within the shell of the POD, the microstimulator implant remains fixed against the Vagus nerve so the electrodes remain in contact with the nerve. The POD anchors the implant in place and prevents the implant from rotating or separating from the nerve, as well as maintaining contact between the electrodes and the nerve and preserving the orientation as necessary for efficient external charging of the microstimulator battery.

Referring back to FIG. **1**C, the system may include an implantable microstimulator contained in a POD, a Patient Charger, and a prescription pad that may be used by the clinician to set dosage parameters for the patient. This system may evaluate the efficacy, safety, and usability of an NCAP technology for chronic treatment of clinical patients. The system can employ a Prescription Pad (external controller) that may include the range of treatment options.

As described in more detail in U.S. Ser. No. 12/874,171 (titled "PRESCRIPTION PAD FOR TREATMENT OF INFLAMMATORY DISORDERS"), previously incorporated by reference in its entirety, the Prescription Pad may incorporate workflows in a simplified interface and provide data collection facilities that can be transferred to an external database utilizing commercially robust and compliant methods and procedures. In use, the system may be recommended for use by a clinician after assessing a patient; the clinician may determine that treatment of chronic inflammation is warranted. The clinician may then refer the patient to an interventional doctor to implant the microstimulator. Thereafter then clinician (or another clinician) may monitor the patient and adjust the device via a wireless programmer (e.g. prescription pad). The clinician may be trained in the diagnosis and treatment procedures for autoimmune and inflammatory disorders; the interventional placement of the system may be performed by a surgeon trained in the implantation of active neurostimulation devices, with a sufficient depth of knowledge and experience regarding cervical and vagal anatomy, experienced in performing surgical dissections in and around the carotid sheath.

The system may output signals, including diagnostics, historical treatment schedules, or the like. The clinician may adjust the device during flares and/or during routine visits. Examples of implantation of the microstimulator were provided in U.S. patent application Ser. No. 12/874,171, which is herein incorporated by reference in its entirety. For example, the implant may be inserted by making an incision in the skin (e.g., ≈3 cm) along Lange's crease between the Facial Vein and the Omohyoid muscle, reflecting the Sternocleidomastoid and gaining access to the carotid sheath. The IJV may be displaced, and the vagus may be dissected from the carotid wall (≤2 cm). A sizing tool may be used to measure the vagus, and an appropriate Microstimulator and POD Kit (small, medium, large) may be selected. The POD may then be inserted under nerve with the POD opening facing the surgeon, so that the microstimulator can be inserted inside POD so that the microstimulator contacts capture the vagus. The POD may then be sutured shut. In some variations a Surgical Tester may be used to activate the microstimulator and perform system integrity and impedance checks, and shut the microstimulator off, during or after the implantation. In other variations the surgical tester may be unnecessary, as described in greater detail below.

A physician may use the Patient Charger to activate the microstimulator, perform integrity checks, and assure sufficient battery reserve exists. Electrodes may be conditioned with sub-threshold current and impedances may be measured. A Physician may charge the microstimulator. In some variations a separate charger (e.g., an "energizer") may be used by the patient directly, separate from the controller the physician may use. Alternatively, the patient controller may include controls for operation by a physician; the system may lock out non-physicians (e.g., those not having a key, code, or other security pass) from operating or modifying the controls.

In general, a physician may establish safe dosage levels. The physician may slowly increment current level to establish a maximum limit (Upper Comfort Limit). This current level may be used to set the Dosage Level. The exact procedure may be determined during this clinical phase.

The Physician may also specify dosing parameters that specify dosage levels and dosage intervals. The device may contain several concurrent dosing programs which may be used to acclimate the patient to stimulus, gradually increase dosage until efficacy is achieved, reset tachyphylaxis, or deal with unique patient situations.

In some variations, the Prescription Pad may be configured to handle multiple patients and may index their data by the microstimulator Serial Number. For example, a Prescription Pad may handle up to 100,000 patients and 10,000 records per patient, and may store the data in its local memory and may be backed up on an external database. In some variations, during each charging session, accumulated even log contents will be uploaded to the Patient Charger for later transfer to Prescription Pad. The data may or may not be cleared from the microstimulator. For example, FIG. **2** shows the addition of a prescription pad **203** wirelessly connected to the charger/programmer **207**.

The microstimulators described herein are configured for implantation and stimulation of the cholinergic anti-inflammatory pathway, and especially the vagus nerve. In particular the microstimulators described herein are configured for implantation in the cervical region of the vagus nerve to provide extremely low duty-cycle stimulation sufficient to modulate inflammation. These microstimulators may be adapted for this purpose by including one or more of the following characteristics, which are described in greater detail herein: the conductive capsule ends of the micro stimulator may be routed to separate electrodes; the conductive capsule ends may be made from resistive titanium alloy to reduce magnetic field absorption; the electrodes may be positioned in a polymer saddle; the device includes a suspension (e.g., components may be suspended by metal clips) to safeguard the electronics from mechanical forces and shock; the device may include an H-bridge current source with capacitor isolation on both leads; the device may include a built in temperature sensor that stops energy absorption from any RF source by detuning the resonator; the device may include a built-in overvoltage sensor to stop energy absorption from any RF source by detuning resonator; the system may include DACs that are used to calibrate silicon for battery charging and protection; the system may include DACs that are used to calibrate silicon for precision timing rather than relying on crystal oscillator; the system may include a load stabilizer that maintains constant load so that inductive system can communicate efficiently; the system may include current limiters to prevent a current rush so that the microstimulator will power up smoothly from resonator power source; the system may extract a clock from carrier OR from internal clock; the device may use an ultra-low power accurate RC oscillator that uses stable temperature in body, DAC calibration, and clock adjustment during charging process; the device may use a solid state LIPON battery that allows fast recharge, supports many cycles, cannot explode, and is easy to charge with constant voltage; and the device may include a resonator that uses low frequency material designed not to absorb energy by high frequency sources such as MRI and Diathermy devices.

Many of these improvements permit the device to have an extremely small footprint and power consumption, while still effectively modulating the vagus nerve.

FIG. **3**A is a perspective drawing of the Pod containing the microstimulator. Sutures (not shown) are intended to be bridged across one to three sets of holes. Electrodes integrated into the pod are not shown but would extend as bands originating and ending on the two outer pairs of suture holes.

In some variations, including those described above, the microstimulator consists of a ceramic body with hermetically sealed titanium-niobium ends and integral platinum-iridium electrodes attached. The microstimulator may be designed to fit within a POD **309**, as shown in FIGS. **3**A-**3**D. As described above, the POD is a biocompatible polymer with integrated electrodes that may help the microstimulator to function as a leadless cuff electrode. In some variations, such as the variation shown in FIG. **3**E, contained within the hermetic space of the microstimulator **301** is an electronic assembly that contains a rechargeable battery **321**, solenoid antenna **323**, hybrid circuit **325** and electrode contacts (Ti Alloy braze ring and end cap) **327** at each end to make contact with the titanium/platinum case ends.

In some embodiments, the microstimulator can be batteryless. The batteryless microstimulator can be powered inductively by an external power source to deliver an electrical stimulus to the nerve. In some embodiments, the batteryless microstimulator can have a capacitor or supercapacitor instead of a battery for storing energy which can be released as an electrical stimulus.

As mentioned above, some of the device variations described herein may be used with a POD to secure the implant (e.g., the leadless/wireless microstimulator implant) in position within the cervical region of the vagus nerve so that the device may be programmed and recharged by the charger/programmer (e.g., "energizer"). For example, FIG. **4** shows a schematic diagram of a POD containing a microstimulator. The cross section in FIG. **4** shows the ceramic tube containing electronic assembly that includes the hybrid, battery and coil. The rigid or semi-rigid contacts are mounted on the tube and surround the oval vagus nerve. The POD surrounds the entire device and includes a metal conductor that makes electrical contact with the microstimulator contacts and electrically surrounds the nerve.

In some variations, the microstimulator may have a bipolar stimulation current source that produce as stimulation dose with the characteristics shown in table 1, below. In some variation, the system may be configured to allow adjustment of the "Advanced Parameters" listed below; in some variations the parameters may be configured so that they are predetermined or pre-set. In some variations, the Advanced Parameters are not adjustable (or shown) to the clinician. All parameters listed in Table 1 are ±5% unless specified otherwise.

TABLE 1

Microstimulator parameters		
Property	Value	Default
Dosage Amplitude (DA)	0-5,000 μA in 25 μA steps	0
Intervals	Minute, Hour, Day, Week, Month	Day
Number of Doses per Interval	N = 60 Maximum	1
Advanced Parameters		
Pulse width Range (PW)	100-1,000 μS in 50 μS increments	200
Stimulus Duration (SD)	0.5-1000 seconds per dose	60
Pulse Frequency	1-50 Hz	10

TABLE 1-continued

Microstimulator parameters		
Property	Value	Default
(PF)		
Stimulus Voltage (SV)	±3.3 or ±5.5 ± 1 Volts	Automatically set by software
Constant Current Output	±15% over supported range of load impedances (200-2000Ω)	
Specific Dose Time	Set a specific time between 12:00 am-12:00 am in one minute increments for each Dose Issue	Driven by default table (TBD)
Number of Sequential Dosing Programs	4 maximum	1

The Dosage Interval is defined as the time between Stimulation Doses. In some variations, to support more advanced dosing scenarios, up to four 'programs' can run sequentially. Each program has a start date and time and will run until the next program starts. Dosing may be suspended while the Prescription Pad is in Programming Mode. Dosing may typically continue as normal while charging. Programs may be loaded into one of four available slots and can be tested before they start running. Low, Typical, and High Dose schedules may be provided. A continuous application schedule may be available by charging every day, or at some other predetermined charging interval. For example, Table 2 illustrates exemplary properties for low, typical and high dose charging intervals:

TABLE 2

low typical and high dose charging intervals	
Property	Value
Low Dose Days Charge Interval	30 days max: 250 μA, 200 μS, 60 s, 24 hr, 10 Hz, ±3.3 V
Typical Dose Charge Interval	30 days max: 1,000 μA, 200 μS, 120 s, 24 hr, 10 Hz, ±3.3 V
High Dose Charge Interval	3.5 days max: 5,000 μA, 500 μS, 240 s, 24 hr, 20 Hz, ±5.5 V,

The system may also be configured to limit the leakage and maximum and minimum charge densities, to protect the patient, as shown in Table 3:

TABLE 3

safety parameters	
Property	Value
Hardware DC Leakage Protection	<50 nA
Maximum Charge Density	30 $\mu C/cm^2$/phase
Maximum Current Density	30 mA/cm^2

In some variations, the system may also be configured to allow the following functions (listed in Table 4, below):

TABLE 4

Additional functions of the microstimulator and/or controller(s)	
Function	Details
Charging	Replenish Battery
Battery Check	Determine charge level
System Check	Self Diagnostics
Relative Temperature	Temperature difference from baseline
Program Management	Read/Write/Modify a dosage parameter programs
Program Up/Download	Transfer entire dosage parameter programs
Electrode Impedances	Bipolar Impedance (Complex)
Signal Strength	Strength of the charging signal to assist the patient in aligning the external Charge to the implanted Microstimulator.
Patient Parameters	Patient Information
Patient History	Limited programming and exception data
Implant Time/Zone	GMT + Time zone, 1 minute resolution, updated by Charger each charge session
Firmware Reload	Boot loader allows complete firmware reload
Emergency Stop	Disable dosing programs and complete power down system until Prescription Pad connected

In some embodiments as shown in FIG. **11**, a transcutaneous electrical nerve stimulator **50** can be used to stimulate the vagus nerve. An example of a transcutaneous electrocial nerve stimulator is described in U.S. Pat. No. 8,843,210 to Simon et al., which is herein incorporated by reference in its entirety for all purposes. The transcutaneous electrical nerve stimulator can be used in place of the implanted microstimulator, or it can be used along with the implanted microstimulator. FIG. **11** illustrates one placement of the stimulator **50** to a target location on the patient's neck. For reference, locations of the following vertebrae are also shown: first cervical vertebra **71**, the fifth cervical vertebra **75**, the sixth cervical vertebra **76**, and the seventh cervical vertebra **77**.

EEG Recording System

FIG. **5** illustrates an EEG recording device **500** with electrodes **502** placed proximate the brain regions of interest, such the NB and/or LC, can be used to record the patient's EEGs. For example, one or more electrodes can be placed on the patient's forehead over the basal forebrain to record EEGs from the NB, while one or more electrodes can be placed on the lower back portion of the patient's head over the brainstem to record EEGs from the LC. P300 can be measured from electrodes being used to measure the NB and/or LC, and/or can be measured from electrodes placed over the parietal lobe. A baseline EEG can be recorded before VNS to serve as a comparison for EEGs measured after VNS.

In some embodiments, the EEG recording device may be programmed to detect and analyze P300 and/or activation of the NB and/or LC. In some embodiments, the analysis of the data from the EEG recording device can be accomplished with a separate computing device programmed to do the task. In some embodiments, the results of this analysis can be communicated to a controller that can adjust one or more stimulation parameters based on the analysis of P300 and/or activation of the NB and/or LC. The controller can be located on the microstimulator, the prescription pad, the energizer, the EEG recording device, or a separate computing device.

Prescreening Patients Using EEG

Activation of the Nucleus Basalis and/or the Locus coeruleus and/or detection of P300, all of which can be detected and/or measured with an EEG, can be used to prescreen subjects likely respond to VNS treatment prior to implantation. EEG recordings can be measured during or following stimulation of the auricular branch of the vagus nerve, or independent of any additional stimulus. The stimulation of the auricular branch of the vagus nerve can be accomplished through electrical stimulation or mechanical stimulation. In some embodiments, the stimulation can be noninvasive. For example, the electrical stimulation or mechanical stimulation can be delivered through the skin by a stimulation device placed on the skin surface of the ear. Alternatively, the stimulation can be invasive using, for example, a needle electrode to deliver electrical stimulation directly to the nerve.

During or after stimulation of the auricular branch of the vagus nerve, EEG recordings can be taken of the NB and/or LC and the presence of P300 can be detected in the EEG recordings. In some embodiments, at least some of the EEG recordings can be taken after VNS without providing any other additional stimulation to elicit P300 or activity in the NB and/or LC. In some embodiments, at least some of the EEG recordings can be taken while eliciting P300 using a predetermined protocol, such as the auditory and/or visual stimulation oddball protocol. If the EEG recordings show activation of the NB and/or the LC and/or P300 is detected in the EEG recordings, then it is likely that the vagus nerve responded to the stimulation and the patient is a suitable candidate for VNS therapy. In some embodiments, for the analysis, a comparison can be made with reference to EEG recordings taken before VNS therapy.

Use case example: A subject with rheumatoid arthritis is being screened for likelihood of response VNS treatment. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during electrical stimulation of the subject's auricular branch of the vagus nerve at maximum tolerated current intensity. The subject will pass the screen should P300 and/or activation of the Nucleus Basalis and/or the Locus coeruleus be detected.

Long Term Potentiation

It has been postulated that analogous to somatotopically organized brain regions that sense pain, there exists an immunological homunculus, whereby the immune system acts as a sensory organ that maps to specific regions within the central nervous system at the terminal of the afferent arm of the inflammatory reflex [7]. As activity within the NB and LC can be induced by VNS, and VNS induces long lasting plasticity within the auditory cortex via activation of the NB and LC, we reasoned that plasticity within the central neural reflexes, in part by this immunological homunculus may be induced by VNS activation of the NB and LC as well.

Therefore, VNS activation of the NB and/or the LC can induce long term potentiation of the inflammatory reflex. Typical VNS parameters include an amplitude of 0.1-3 mA, frequency of 1 Hz-30 Hz, pulse width of 100 uS-500 uS, duration of 0.5 second to 10 minutes in duration. The off time between stimulations can be greater than 2, 4, 8, 12, 24, and 48 hours. These parameters are suitable for use in any of the embodiments described herein. For example, a 100 us charge balanced biphasic pulse can be delivered with a current of 0.8 mA as a train of 15 pulses at 30 Hz with a 500 ms train duration. The amplitude and other parameters can be ramped up over time, maintained at a constant level, or be modulated based on feedback, which can be based on NB and/or LC activity and/or detection of P300, for example. NB and/or LC and/or P300 activity can be detected by monitoring, measuring, and/or quantifying electrical activity from those brain regions with EEG recordings.

Feedback Control of VNS

EEG measurements of P300, and/or EEG measurements to detect activation of the Nucleus Basalis and/or the Locus coeruleus can be used to provide immediate or rapid feedback on stimulation parameters during programming or reprogramming of an implanted VNS device. Various stimulation parameters may be increased, decreased or otherwise adjusted until activation of NB, LC or P300 is detected. Feedback control can be used in an open loops system or a closed loop system as described below.

FIG. **6** illustrates a flow chart that describes a method for modulating vagus nerve stimulation using feedback from EEG recordings. For example, this flow chart can be used to treat a patient that is not responding well to VNS treatment. The vagus nerve can be stimulated in step **600** and then EEG recordings can be taken in step **602**. The EEG recordings can be taken during the VNS, and can also be taken after the VNS. Next, in step **604**, the EEG is analyzed for P300 and/or activation of the NB and/or LC. In some embodiments, the analysis can be performed by a physician, while in other embodiments, the analysis can be performed by a computing device with filters and algorithms tailored to detecting those specific EEG features. At step **606**, a decision is made based on the analysis in step **604** whether P300 is detected and/or activation of the NB and/or the LC is detected from the EEG recordings. If P300 and/or activation of the NB and/or the LC is not detected, then the VNS parameters are adjusted, by for example increasing the amplitude and/or the duration of the stimulation in step **608**. After the VNS parameters are adjusted, the process loops back to step **600**. If at step **606** it is determined that P300 is detected and/or activation of the NB and/or LC is detected, then the VNS parameters can be set to the current stimulation parameters. In some embodiments, this can be performed manually by the physician or health care provider, while in other embodiments, the parameters can be set automatically by a computing device performing the analysis of the EEG recordings.

FIG. **7** illustrates a flow chart that describes another method for modulating vagus nerve stimulation using feedback from EEG recordings. This flow chart is particularly suited for reducing the intensity of the VNS treatment in a patient that is responding well to VNS. By reducing the intensity of the VNS treatment, the patient's pain can be reduced and comfort can be improved. In step **700**, the patient's response to VNS treatment is determined. If the patient is not responding well to VNS, then this treatment protocol is not suitable and the process ends in step **702**. If the patient is responding well to VNS, then the process proceeds to step **704** where EEG recordings are taken. Next, in step **706**, the physician or a computing device analyzes and characterizes the EEG recordings for P300 and/or activation of the NB and/or the LC. Then, in step **708**, the VNS parameters can be adjusted, by for example, decreasing the amplitude or the duration of the stimulation. In step **710**, the vagus nerve is stimulated using the adjusted parameters. In step **712**, another set of EEG recordings are taken. In step **714**, the EEG recordings can be analyzed and characterized to determine whether P300 and/or activation of the NB and/or LC are present and/or are above thresholds. The thresholds can be predetermined or can be based on the initial characterization of the EEG recordings performed in step **706**. If P300 and/or activation of the NB and/or LC is still detected and/or are still above the thresholds, then the process loops back to step **708** wherein the stimulation parameters can be further adjusted, for example, by again decreasing amplitude and/or duration. If in step **714**, P300 and/or activation of the NB and/or LC is not detected and/or falls below the threshold, then the stimulation parameters can be set to a previous set of stimulation parameters, as shown in step **716**, wherein P300 and/or activation of NB and/or LC were detected and/or above the threshold.

FIG. **8** illustrates a flow chart that describes yet another method for modulating vagus nerve stimulation using feedback from EEG recordings. This flow chart is particularly suitable for a patient that is responding well to VNS therapy who wishes to increase the interval between stimulations (the off time). In step **800**, the patient is checked to determine whether the patient is responding well to VNS. If not, the process is not suitable and is ended in step **802**. If the patient is responding well to VNS, the process proceeds to step **804** where EEG recordings are taken. In step **806**, the EEG recordings are analyzed and characterized for P300 and/or activation of the NB and/or LC. In step **808**, the vagus nerve stimulation parameters are adjusted by, for example, increasing the amplitude and/or duration. In step **810**, the vagus nerve can be stimulated using the adjusted parameters, and EEG recordings can be taken in step **812**. In step **814**, the EEG recordings are analyzed and characterized to determine whether P300 and/or activation of the NB and/or the LC is detected and/or above threshold values. The threshold values can be predetermined or can be determined based on a comparison with a baseline EEG, such as the EEG recordings taken in step **804** and analyzed and characterized in step **806**. If the determination in step **812** is that P300 and/or activation of the NB and/or the LC is not detected and/or falls below the threshold values, then the process loops back to step **808** where the VNS parameters are adjusted by, for example, further increasing the amplitude and/or duration. If the determination in step **812** is that P300 and/or activation of the NB and/or the LC is detected and/or falls above the threshold values, then the VNS parameters can be set to the current stimulation parameters and the off time between stimulations can be increased, as shown in step **816**. In some embodiments, the off time can be increased by at least 4, 6, 8, 12, 24, 36, or 48 hours.

Use case example A: A subject with rheumatoid arthritis is not responding to VNS treatment. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during delivery of test doses. Stimulation dose will increase in intensity, such as amplitude, until change in P300 and activation of the Nucleus Basalis and/or the Locus coeruleus is detected. The physician will then program the applicable stimulation parameters for scheduled dosing.

Use case example B: A subject with rheumatoid arthritis is responding well to once daily VNS treatment. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during delivery of test doses. Stimulation dose will decrease in intensity, such as amplitude, until change in P300 and activation of the Nucleus Basalis and/or the Locus coeruleus is detected. The physician will then program the applicable stimulation parameters for scheduled dosing.

Use case example C: A subject with rheumatoid arthritis is responding well to once daily VNS treatment. The physician intends to decrease the weekly frequency of stimulation. The physician will record P300 and EEG measurements of activation of the Nucleus Basalis and/or the Locus coeruleus during delivery of test doses. Stimulation dose will increase in intensity, such as amplitude, until change in P300 and activation of the Nucleus Basalis and/or the Locus coeruleus is detected. The physician will then program a greater interval between doses of stimulation.

A closed loop system can include an EEG device, an implantable nerve stimulator (e.g. vagus nerve), a prescription pad and an energizer. The EEG device can measure intracranial potentials and interpret P300, and/or activation of the Nucleus Basalis and/or the Locus coeruleus. The EEG device can communicate through wire or wirelessly, e.g. by Bluetooth protocol, to the prescription pad or energizer which programs stimulation parameters into the implantable nerve stimulator. A controller within the prescription pad, energizer, or EEG device can adjust one or more stimulation parameters, e.g. pulse width, pulse amplitude, pulse frequency, which can be programmed and carried out by the nerve stimulator. For example, the controller can be programmed to increase various stimulation parameters, such as amplitude, until P300 and/or activation of the NB and/or LC is detected by the EEG device. In some embodiments, the controller can be programmed to increase the interval, e.g. the off time, between doses of VNS when P300 and/or activation of the NB and/or LC is detected. In some embodiments, the controller can be programmed to decrease various stimulation parameters, such as amplitude, when P300 and/or activation of the NB and/or LC is detected.

Deep Brain Stimulation and Transcranial Magnetic Stimulation

In some embodiments, deep brain stimulation and/or transcranial magnetic stimulation of Nucleus Basalis and/or the Locus coeruleus can be used to treat chronic inflammatory disease, e.g. rheumatoid arthritis and Crohn's disease. As described above, stimulation of the NB and LC can be used to induce long term potentiation of the inflammatory reflex. In some variations, the deep brain stimulation and trans-cranial magnetic stimulation directly activates the anti-inflammatory reflex. In some embodiments, the deep brain stimulation and/or transcranial magnetic stimulation can be used in conjunction of VNS, while in other embodiments, it can be used without VNS to directly activate the inflammatory reflex through stimulation of the NB and LC. In some embodiments, if used with VNS, the deep brain stimulation and/or transcranial magnetic stimulation can be delivered prior to the VNS to first potentiate the inflammatory reflex before delivering the VNS. In other embodiments, if used with VNS, the deep brain stimulation and/or transcranial magnetic stimulation can be delivered concurrently with the VNS to potentiate the inflammatory reflex while delivering the VNS.

FIG. **9** illustrates a deep brain stimulator **900** that can be implanted with electrodes **902**, **904** positioned at the NB and/or LC, thereby allowing the stimulator **900** to deliver electrical stimulation to the NB and/or LC. The stimulation can be delivered using stimulation parameters of about 10-10,000 uA, 50-500 Hz for 5-120 minutes per session. Sessions can be given at a frequency of twice/day, once/day, once/two days, once/three days, once/four days, once/five days, once/six days, and once/seven days, once/14 days, and once/month.

In some embodiments, as illustrated in FIG. **10**, a transcranial magnetic stimulator **1000** can be used to stimulate the NB and/or LC. The transcranial magnetic stimulator can have one or more coils **1002**, **1004** that generate a magnetic field for stimulating the NB and/or LC. The depth of penetration of the magnetic field can be tailored to focus the magnetic field on the NB and/or LC. The stimulation can be provided at either low frequency (<3 Hz) or high frequency (3-25 Hz) for 5 minutes to 120 minutes per session with a magnetic field of up to about 3 Tesla. Sessions can be given at a frequency of twice/day, once/day, once/two days, once/three days, once/four days, once/five days, once/six days, and once/seven days, once/14 days, and once/month.

Use case example A: At least one electrode is implanted into the Nucleus Basalis and/or the Locus coeruleus of a subject with a chronic inflammatory disease, e.g. rheumatoid arthritis. The brain, specifically the NB and/or LC, is stimulated with electrical current, eg. 10-100 uA, 50-500 Hz for 5 minutes to 1 hr per session.

Use case example B: A trans-cranial magnetic coil is oriented for stimulation into the Nucleus Basalis and/or the Locus coeruleus of a subject with a chronic inflammatory disease, e.g. rheumatoid arthritis. The brain, specifically the NB and/or the LC, is stimulated with at either low frequency (<3 Hz) or high frequency (3-25 Hz) for 5 minutes to 1 hr per session with a magnetic field of up to about 3 Tesla.

It is understood that this disclosure, in many respects, is only illustrative of the numerous alternative device embodiments of the present invention. Changes may be made in the details, particularly in matters of shape, size, material and arrangement of various device components without exceeding the scope of the various embodiments of the invention. Those skilled in the art will appreciate that the exemplary embodiments and descriptions thereof are merely illustrative of the invention as a whole. While several principles of the invention are made clear in the exemplary embodiments described above, those skilled in the art will appreciate that modifications of the structure, arrangement, proportions, elements, materials and methods of use, may be utilized in the practice of the invention, and otherwise, which are particularly adapted to specific environments and operative requirements without departing from the scope of the invention. In addition, while certain features and elements have been described in connection with particular embodiments, those skilled in the art will appreciate that those features and elements can be combined with the other embodiments disclosed herein.

What is claimed is:

1. A system for stimulating a nerve of a patient, the system comprising:

- an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of programmed stimulation parameters;
- an EEG recording device configured to record an EEG of the patient; and
- a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of: a presence of P300, an activation of a nucleus basalis, and an activation of a locus coeruleus is indicated by the EEG, and adjust the set of programmed stimulation parameters based on the determination of whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG,
- wherein adjusting the set of programmed stimulation parameters includes decreasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of stimulation if the EEG indicates at least one of: the presence of P300, the activation of the nucleus basalis, and the activation of the locus coeruleus.

2. The system of claim **1**, wherein the controller is located in a prescription pad.

3. The system of claim **1**, wherein the controller is located in an energizer configured to provide power to the implantable nerve stimulator.

4. The system of claim **1**, wherein the controller is located in the EEG recording device.

5. The system of claim **1**, wherein the set of programmed stimulation parameters comprises a pulse amplitude, a pulse width, and a pulse frequency.

6. The system of claim **1**, wherein the system is configured to induce long term potentiation of an inflammatory reflex in the patient.

7. The system of claim **1**, wherein the controller is configured to wirelessly communicate with the implantable nerve stimulator.

8. The system of claim **1**, wherein the implantable nerve stimulator is configured to be positioned around the nerve of the patient.

9. A system for stimulating a nerve of a patient, the system comprising:

- an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of programmed stimulation parameters;
- an EEG recording device configured to record an EEG of the patient; and
- a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of: a presence of P300, an activation of a nucleus basalis, and an activation of a locus coeruleus is indicated by the EEG, and adjust the set of programmed stimulation parameters based on the determination of whether at least one of P300, activation of the nucleus basalis, and activation of the locus coeruleus is indicated by the EEG,
- wherein adjusting the set of programmed stimulation parameters includes increasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of stimulation if the EEG does not indicate at least one of: the presence of P300, the activation of the nucleus basalis, and the activation of the locus coeruleus.

10. A system for stimulating a nerve of a patient, the system comprising:

- an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of stimulation parameters;
- an EEG recording device configured to record an EEG of the patient; and
- a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of a nucleus basalis and a locus coeruleus is activated as indicated by the EEG, and adjust the set of stimulation parameters based on the determination of whether at least one of the nucleus basalis and the locus coeruleus is activated as indicated by the EEG,
- wherein adjusting the set of stimulation parameters includes decreasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of stimulation if the EEG indicates activation of at least one of the nucleus basalis and the locus coeruleus,
- wherein the controller is configured to repeatedly determine whether at least one of the nucleus basalis and the locus coeruleus is activated, and adjust the set of stimulation parameters until a dose of stimulation is at a level necessary to modulate an inflammatory reflex of the patient.

11. The system of claim **10**, wherein the controller is configured to wirelessly communicate with the implantable nerve stimulator.

12. The system of claim **10**, wherein the controller is located in a prescription pad.

13. The system of claim **10**, further comprising an energizer configured to provide power to the implantable nerve stimulator.

14. The system of claim **13**, wherein the energizer is configured to inductively charge the implantable nerve stimulator.

15. The system of claim **10**, wherein the set of programmed stimulation parameters comprises a pulse amplitude, a pulse width, a pulse frequency, and a duration.

16. The system of claim **10**, wherein the implantable nerve stimulator is configured to be positioned around the nerve of the patient.

17. A system for stimulating a nerve of a patient, the system comprising:

an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of stimulation parameters;

an EEG recording device configured to record an EEG of the patient; and

a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of a nucleus basalis and a locus coeruleus is activated as indicated by the EEG, and adjust the set of stimulation parameters based on the determination of whether at least one of the nucleus basalis and the locus coeruleus is activated as indicated by the EEG,

wherein the controller is configured to repeatedly determine whether at least one of the nucleus basalis and the locus coeruleus is activated, and adjust the set of stimulation parameters until a dose of stimulation is at a level necessary to modulate an inflammatory reflex of the patient,

wherein adjusting the set of stimulation parameters includes increasing one or more of an amplitude, a pulse width, a pulse frequency and a duration of the stimulation if the EEG does not indicate activation of at least one of the nucleus basalis and the locus coeruleus.

18. A system for stimulating a nerve of a patient, the system comprising:

an implantable nerve stimulator configured to stimulate the nerve of the patient according to a set of stimulation parameters;

an EEG recording device configured to record an EEG of the patient; and

a controller in communication with both the EEG recording device and the implantable nerve stimulator, the controller programmed to determine whether at least one of a nucleus basalis and a locus coeruleus is activated as indicated by the EEG, and adjust the set of stimulation parameters based on the determination of whether at least one of the nucleus basalis and the locus coeruleus is activated as indicated by the EEG,

wherein the controller is configured to repeatedly determine whether at least one of: the presence of P300, the activation of the nucleus basalis, and the activation of the locus coeruleus is indicated by the EEG, and adjust the set of stimulation parameters until a dose of stimulation is at a minimum level necessary to modulate an inflammatory reflex of the patient.

19. The system of claim **18**, further comprising an energizer configured to provide power to the implantable nerve stimulator.

20. The system of claim **19**, wherein the energizer is configured to inductively charge the implantable nerve stimulator.

* * * * *