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Detecting, assessing and managing extreme seizure events

Abstract

Methods, system and apparatus for identifying an extreme epileptic state/event in a patient are provided. In one aspect, at least two seizure events are identified. At least one inter-seizure interval (ISI) value related to the at least two seizure events are determined. The ISI value is compared to at least one reference value. An occurrence of an extreme seizure event is determined based upon the comparison of the determined ISI value to the at least one reference value. In another aspect, a first seizure event is detected. At least one body index affected by the first seizure event is determined. A second seizure event is detected. An occurrence of an extreme seizure event is determined based at least in part in response to a determination that the second seizure event occurred prior to the body index value returning to a reference value.

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References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
4172459	12/1978	Hepp	N/A	N/A
4197856	12/1979	Northrop	N/A	N/A
4291699	12/1980	Geddes et al.	N/A	N/A
4295474	12/1980	Fischell	N/A	N/A
4320766	12/1981	Alihanka et al.	N/A	N/A
4541432	12/1984	Molina-Negro et al.	N/A	N/A
4573481	12/1985	Bullara	N/A	N/A
4702254	12/1986	Zabara	N/A	N/A
4867164	12/1988	Zabara	N/A	N/A
4920979	12/1989	Bullara	N/A	N/A
4949721	12/1989	Toriu et al.	N/A	N/A
4979511	12/1989	Terry, Jr.	N/A	N/A
5025807	12/1990	Zabara	N/A	N/A
5062169	12/1990	Kennedy et al.	N/A	N/A
5113869	12/1991	Nappholz et al.	N/A	N/A
5137020	12/1991	Wayne et al.	N/A	N/A
5154172	12/1991	Terry, Jr. et al.	N/A	N/A
5179950	12/1992	Stanislaw	N/A	N/A
5186170	12/1992	Varrichio et al.	N/A	N/A
5188104	12/1992	Wernicke et al.	N/A	N/A
5194847	12/1992	Taylor et al.	N/A	N/A
5203326	12/1992	Collins	N/A	N/A
5205285	12/1992	Baker, Jr.	N/A	N/A
5213568	12/1992	Lattin et al.	N/A	N/A

5215086	12/1992	Terry, Jr. et al.	N/A	N/A
5215089	12/1992	Baker, Jr.	N/A	N/A
5222494	12/1992	Baker, Jr.	N/A	N/A
5231988	12/1992	Wernicke et al.	N/A	N/A
5235980	12/1992	Varrichio et al.	N/A	N/A
5237991	12/1992	Baker, Jr. et al.	N/A	N/A
5243980	12/1992	Mehra	N/A	N/A
5251634	12/1992	Weinberg	N/A	N/A
5263480	12/1992	Wernicke et al.	N/A	N/A
5269302	12/1992	Swartz et al.	N/A	N/A
5269303	12/1992	Wernicke et al.	N/A	N/A
5299569	12/1993	Wernicke et al.	N/A	N/A
5304206	12/1993	Baker, Jr. et al.	N/A	N/A
5307263	12/1993	Brown	N/A	N/A
5311876	12/1993	Olsen et al.	N/A	N/A
5313953	12/1993	Yomtov et al.	N/A	N/A
5330507	12/1993	Schwartz	N/A	N/A
5330515	12/1993	Rutecki et al.	N/A	N/A
5334221	12/1993	Bardy	N/A	N/A
5335657	12/1993	Terry, Jr. et al.	N/A	N/A
5357427	12/1993	Langen et al.	N/A	N/A
5404877	12/1994	Nolan et al.	N/A	N/A
5425373	12/1994	Causey, III	N/A	N/A
5441047	12/1994	David et al.	N/A	N/A
5513649	12/1995	Gevins et al.	N/A	N/A
5522862	12/1995	Testerman et al.	N/A	N/A
5523742	12/1995	Simkins et al.	N/A	N/A
5531778	12/1995	Maschino et al.	N/A	N/A
5540730	12/1995	Terry, Jr. et al.	N/A	N/A
5540734	12/1995	Zabara	N/A	N/A
5544649	12/1995	David et al.	N/A	N/A
5544661	12/1995	Davis et al.	N/A	N/A
5553609	12/1995	Chen et al.	N/A	N/A
5571150	12/1995	Wernicke et al.	N/A	N/A
5601435	12/1996	Quy	N/A	N/A
5610590	12/1996	Johnson et al.	N/A	N/A
5611350	12/1996	John	N/A	N/A
5645077	12/1996	Foxlin	N/A	N/A
5645570	12/1996	Corbucci	N/A	N/A
5651378	12/1996	Matheny et al.	N/A	N/A
5658318	12/1996	Stroetmann et al.	N/A	N/A
5683422	12/1996	Rise	N/A	N/A
5690681	12/1996	Geddes et al.	N/A	N/A
5690688	12/1996	Noren et al.	N/A	N/A
5700282	12/1996	Zabara	N/A	N/A
5707400	12/1997	Terry, Jr. et al.	N/A	N/A
5716377	12/1997	Rise et al.	N/A	N/A
5720771	12/1997	Snell	N/A	N/A
5722999	12/1997	Snell	N/A	N/A
5743860	12/1997	Hively et al.	N/A	N/A

5748113	12/1997	Torch	N/A	N/A
5759199	12/1997	Snell et al.	N/A	N/A
5792186	12/1997	Rise	N/A	N/A
5800474	12/1997	Benabid et al.	N/A	N/A
5807284	12/1997	Foxlin	N/A	N/A
5808552	12/1997	Wiley et al.	N/A	N/A
5833709	12/1997	Rise et al.	N/A	N/A
5853005	12/1997	Scanlon	N/A	N/A
5879309	12/1998	Johnson et al.	N/A	N/A
5905436	12/1998	Dwight et al.	N/A	N/A
5913876	12/1998	Taylor et al.	N/A	N/A
5916181	12/1998	Socci et al.	N/A	N/A
5916239	12/1998	Geddes et al.	N/A	N/A
5928272	12/1998	Adkins et al.	N/A	N/A
5941906	12/1998	Barreras, Sr. et al.	N/A	N/A
5942979	12/1998	Luppino	N/A	N/A
5978702	12/1998	Ward et al.	N/A	N/A
5978972	12/1998	Stewart et al.	N/A	N/A
5987352	12/1998	Klein et al.	N/A	N/A
5995868	12/1998	Dorfmeister et al.	N/A	N/A
6016449	12/1999	Fischell et al.	N/A	N/A
6018682	12/1999	Rise	N/A	N/A
6048324	12/1999	Socci et al.	N/A	N/A
6061593	12/1999	Fischell et al.	N/A	N/A
6073048	12/1999	Kieval et al.	N/A	N/A
6083249	12/1999	Familoni	N/A	N/A
6091992	12/1999	Bourgeois et al.	N/A	N/A
6095991	12/1999	Krausman et al.	N/A	N/A
6104956	12/1999	Naritoku et al.	N/A	N/A
6115628	12/1999	Stadler et al.	N/A	N/A
6115630	12/1999	Stadler et al.	N/A	N/A
6128538	12/1999	Fischell et al.	N/A	N/A
6134474	12/1999	Fischell et al.	N/A	N/A
6162191	12/1999	Foxlin	N/A	N/A
6163281	12/1999	Torch	N/A	N/A
6167311	12/1999	Rezai	N/A	N/A
6171239	12/2000	Humphrey	N/A	N/A
6175764	12/2000	Loeb et al.	N/A	N/A
6205359	12/2000	Boveja	N/A	N/A
6208894	12/2000	Schulman et al.	N/A	N/A
6208902	12/2000	Boveja	N/A	N/A
6221908	12/2000	Kilgard et al.	N/A	N/A
6246344	12/2000	Torch	N/A	N/A
6248080	12/2000	Miesel et al.	N/A	N/A
6253109	12/2000	Gielen	N/A	N/A
6264614	12/2000	Albert et al.	N/A	N/A
6269270	12/2000	Boveja	N/A	N/A
6272379	12/2000	Fischell et al.	N/A	N/A
6304775	12/2000	Iasemidis et al.	N/A	N/A
6315740	12/2000	Singh	N/A	N/A

6324421	12/2000	Stadler et al.	N/A	N/A
6337997	12/2001	Rise	N/A	N/A
6339725	12/2001	Naritoku et al.	N/A	N/A
6341236	12/2001	Osorio et al.	N/A	N/A
6356784	12/2001	Lozano et al.	N/A	N/A
6356788	12/2001	Boveja	N/A	N/A
6358203	12/2001	Bardy	N/A	N/A
6361507	12/2001	Foxlin	N/A	N/A
6361508	12/2001	Johnson et al.	N/A	N/A
6366813	12/2001	DiLorenzo	N/A	N/A
6366814	12/2001	Boveja et al.	N/A	N/A
6374140	12/2001	Rise	N/A	N/A
6397100	12/2001	Stadler et al.	N/A	N/A
6427086	12/2001	Fischell et al.	N/A	N/A
6429217	12/2001	Puskas	N/A	N/A
6441731	12/2001	Hess	N/A	N/A
6449512	12/2001	Boveja	N/A	N/A
6459936	12/2001	Fischell et al.	N/A	N/A
6463328	12/2001	John	N/A	N/A
6466822	12/2001	Pless	N/A	N/A
6473639	12/2001	Fischell et al.	N/A	N/A
6473644	12/2001	Terry, Jr. et al.	N/A	N/A
6477418	12/2001	Plicchi et al.	N/A	N/A
6480743	12/2001	Kirkpatrick et al.	N/A	N/A
6484132	12/2001	Hively et al.	N/A	N/A
6497655	12/2001	Linberg et al.	N/A	N/A
6501983	12/2001	Natarajan et al.	N/A	N/A
6505074	12/2002	Boveja et al.	N/A	N/A
6532388	12/2002	Hill et al.	N/A	N/A
6539263	12/2002	Schiff et al.	N/A	N/A
6542081	12/2002	Torch	N/A	N/A
6542774	12/2002	Hill et al.	N/A	N/A
6549804	12/2002	Osorio et al.	N/A	N/A
6556868	12/2002	Naritoku et al.	N/A	N/A
6560486	12/2002	Osorio et al.	N/A	N/A
6564102	12/2002	Boveja	N/A	N/A
6587719	12/2002	Barrett et al.	N/A	N/A
6587727	12/2002	Osorio et al.	N/A	N/A
6594524	12/2002	Esteller et al.	N/A	N/A
6599250	12/2002	Webb et al.	N/A	N/A
6600956	12/2002	Maschino et al.	N/A	N/A
6609025	12/2002	Barrett et al.	N/A	N/A
6610713	12/2002	Tracey	N/A	N/A
6611715	12/2002	Boveja	N/A	N/A
6611783	12/2002	Kelly, Jr. et al.	N/A	N/A
6615081	12/2002	Boveja	N/A	N/A
6615085	12/2002	Boveja	N/A	N/A
6622038	12/2002	Barrett et al.	N/A	N/A
6622041	12/2002	Terry, Jr. et al.	N/A	N/A
6622047	12/2002	Barrett et al.	N/A	N/A

6628985	12/2002	Sweeney et al.	N/A	N/A
6628987	12/2002	Hill et al.	N/A	N/A
6629990	12/2002	Putz et al.	N/A	N/A
6647296	12/2002	Fischell et al.	N/A	N/A
6656125	12/2002	Misczynski et al.	N/A	N/A
6656960	12/2002	Puskas	N/A	N/A
6668191	12/2002	Boveja	N/A	N/A
6671555	12/2002	Gielen et al.	N/A	N/A
6671556	12/2002	Osorio et al.	N/A	N/A
6684105	12/2003	Cohen et al.	N/A	N/A
6721603	12/2003	Zabara et al.	N/A	N/A
6730047	12/2003	Socci et al.	N/A	N/A
6731979	12/2003	MacDonald	N/A	N/A
6735474	12/2003	Loeb et al.	N/A	N/A
6738671	12/2003	Christophersom et al.	N/A	N/A
6760626	12/2003	Boveja	N/A	N/A
6763256	12/2003	Kimball et al.	N/A	N/A
6768969	12/2003	Nikitin et al.	N/A	N/A
6786877	12/2003	Foxlin	N/A	N/A
6788975	12/2003	Whitehurst et al.	N/A	N/A
6793670	12/2003	Osorio et al.	N/A	N/A
6819953	12/2003	Yonce et al.	N/A	N/A
6819956	12/2003	DiLorenzo	N/A	N/A
6832114	12/2003	Whitehurst et al.	N/A	N/A
6836685	12/2003	Fitz	N/A	N/A
6850601	12/2004	Jones, III et al.	N/A	N/A
6879850	12/2004	Kimball	N/A	N/A
6885888	12/2004	Rezai	N/A	N/A
6904390	12/2004	Nikitin et al.	N/A	N/A
6920357	12/2004	Osorio et al.	N/A	N/A
6923784	12/2004	Stein	N/A	N/A
6931274	12/2004	Williams	N/A	N/A
6934580	12/2004	Osorio et al.	N/A	N/A
6934585	12/2004	Schloss et al.	N/A	N/A
6944501	12/2004	Pless	N/A	N/A
6957107	12/2004	Rogers et al.	N/A	N/A
6959215	12/2004	Gliner et al.	N/A	N/A
6961618	12/2004	Osorio et al.	N/A	N/A
6976958	12/2004	Quy	N/A	N/A
6984993	12/2005	Ariav	N/A	N/A
6985771	12/2005	Fischell et al.	N/A	N/A
6990377	12/2005	Gliner et al.	N/A	N/A
7006859	12/2005	Osorio et al.	N/A	N/A
7006872	12/2005	Gielen et al.	N/A	N/A
7010351	12/2005	Firlik et al.	N/A	N/A
7024247	12/2005	Gliner et al.	N/A	N/A
7035684	12/2005	Lee	N/A	N/A
7043305	12/2005	KenKnight et al.	N/A	N/A
7047074	12/2005	Connelly et al.	N/A	N/A

7054686	12/2005	MacDonald	N/A	N/A
7054792	12/2005	Frei et al.	N/A	N/A
7058453	12/2005	Nelson et al.	N/A	N/A
7068842	12/2005	Liang et al.	N/A	N/A
7076288	12/2005	Skinner	N/A	N/A
7077810	12/2005	Lange et al.	N/A	N/A
7079977	12/2005	Osorio et al.	N/A	N/A
7089059	12/2005	Pless	N/A	N/A
7104947	12/2005	Riehl	N/A	N/A
7110820	12/2005	Tcheng et al.	N/A	N/A
7112319	12/2005	Broderick et al.	N/A	N/A
7127370	12/2005	Kelly, Jr. et al.	N/A	N/A
7134996	12/2005	Bardy	N/A	N/A
7139677	12/2005	Hively	N/A	N/A
7146211	12/2005	Frei et al.	N/A	N/A
7146217	12/2005	Firlik et al.	N/A	N/A
7146218	12/2005	Esteller et al.	N/A	N/A
7149572	12/2005	Frei et al.	N/A	N/A
7156808	12/2006	Quy	N/A	N/A
7156809	12/2006	Quy	N/A	N/A
7164941	12/2006	Misczynski et al.	N/A	N/A
7167743	12/2006	Heruth et al.	N/A	N/A
7167750	12/2006	Knudson et al.	N/A	N/A
7174206	12/2006	Frei et al.	N/A	N/A
7177678	12/2006	Osorio et al.	N/A	N/A
7188053	12/2006	Nikitin et al.	N/A	N/A
RE39539	12/2006	Torch	N/A	N/A
7204833	12/2006	Osorio et al.	N/A	N/A
7209786	12/2006	Brockway et al.	N/A	N/A
7209787	12/2006	DiLorenzo	N/A	N/A
7221981	12/2006	Gliner	N/A	N/A
7228167	12/2006	Kara et al.	N/A	N/A
7231254	12/2006	DiLorenzo	N/A	N/A
7236830	12/2006	Gliner	N/A	N/A
7236831	12/2006	Firlik et al.	N/A	N/A
7242983	12/2006	Frei et al.	N/A	N/A
7242984	12/2006	DiLorenzo	N/A	N/A
7254439	12/2006	Misczynski et al.	N/A	N/A
7263467	12/2006	Sackellares et al.	N/A	N/A
7274298	12/2006	Frank	N/A	N/A
7277758	12/2006	DiLorenzo	N/A	N/A
7280867	12/2006	Frei et al.	N/A	N/A
7282030	12/2006	Frei et al.	N/A	N/A
7289844	12/2006	Misczynski et al.	N/A	N/A
7292890	12/2006	Whitehurst et al.	N/A	N/A
7295881	12/2006	Cohen et al.	N/A	N/A
7299096	12/2006	Balzer et al.	N/A	N/A
7302298	12/2006	Lowry et al.	N/A	N/A
7304580	12/2006	Sullivan et al.	N/A	N/A
7305268	12/2006	Gliner et al.	N/A	N/A

7313440	12/2006	Miesel	N/A	N/A
7314451	12/2007	Halperin et al.	N/A	N/A
7321837	12/2007	Osorio et al.	N/A	N/A
7324850	12/2007	Persen et al.	N/A	N/A
7324851	12/2007	DiLorenzo	N/A	N/A
7330760	12/2007	Heruth et al.	N/A	N/A
7346391	12/2007	Osorio et al.	N/A	N/A
7353063	12/2007	Simms, Jr.	N/A	N/A
7353064	12/2007	Gliner et al.	N/A	N/A
7373199	12/2007	Sackellares et al.	N/A	N/A
7385443	12/2007	Denison	N/A	N/A
7389144	12/2007	Osorio et al.	N/A	N/A
7389147	12/2007	Wahlstrand et al.	N/A	N/A
7395113	12/2007	Heruth et al.	N/A	N/A
7395216	12/2007	Rosenfeld et al.	N/A	N/A
7401008	12/2007	Frei et al.	N/A	N/A
7403820	12/2007	DiLorenzo	N/A	N/A
7420472	12/2007	Tran	N/A	N/A
7433732	12/2007	Carney et al.	N/A	N/A
7437196	12/2007	Wyler et al.	N/A	N/A
7447545	12/2007	Heruth et al.	N/A	N/A
7454245	12/2007	Armstrong et al.	N/A	N/A
7483747	12/2008	Gliner et al.	N/A	N/A
7488293	12/2008	Marcovecchio et al.	N/A	N/A
7488294	12/2008	Torch	N/A	N/A
7491181	12/2008	Heruth et al.	N/A	N/A
7494464	12/2008	Rzesnitzek et al.	N/A	N/A
7502643	12/2008	Farringdon et al.	N/A	N/A
7515054	12/2008	Torch	N/A	N/A
7539532	12/2008	Tran	N/A	N/A
7539533	12/2008	Tran	N/A	N/A
7539543	12/2008	Schiff et al.	N/A	N/A
7558622	12/2008	Tran	N/A	N/A
7565132	12/2008	Ben Ayed	N/A	N/A
7590453	12/2008	Heruth et al.	N/A	N/A
7620456	12/2008	Gliner et al.	N/A	N/A
7629890	12/2008	Sullivan et al.	N/A	N/A
7643655	12/2009	Liang et al.	N/A	N/A
7647121	12/2009	Wahlstrand et al.	N/A	N/A
7658112	12/2009	Nakamura	N/A	N/A
7666151	12/2009	Sullivan et al.	N/A	N/A
7714757	12/2009	Denison et al.	N/A	N/A
7717848	12/2009	Heruth et al.	N/A	N/A
RE41376	12/2009	Torch	N/A	N/A
7733224	12/2009	Tran	N/A	N/A
7747318	12/2009	John et al.	N/A	N/A
7761145	12/2009	Virag et al.	N/A	N/A
7769464	12/2009	Gerber et al.	N/A	N/A
7775993	12/2009	Heruth et al.	N/A	N/A
7792583	12/2009	Miesel et al.	N/A	N/A

7801603	12/2009	Westlund et al.	N/A	N/A
7801618	12/2009	Pless	N/A	N/A
7801743	12/2009	Graves et al.	N/A	N/A
7813802	12/2009	Tcheng et al.	N/A	N/A
7822481	12/2009	Gerber et al.	N/A	N/A
7827011	12/2009	DeVaul et al.	N/A	N/A
7831305	12/2009	Gliner	N/A	N/A
7847628	12/2009	Denison	N/A	N/A
7866212	12/2010	Ariav et al.	N/A	N/A
7899545	12/2010	John	N/A	N/A
7935076	12/2010	Estes et al.	N/A	N/A
RE42471	12/2010	Torch	N/A	N/A
7957809	12/2010	Bourget et al.	N/A	N/A
7965833	12/2010	Meir et al.	N/A	N/A
7974671	12/2010	Fujiwara et al.	N/A	N/A
7996076	12/2010	Burns et al.	N/A	N/A
7999857	12/2010	Bunn et al.	N/A	N/A
8000789	12/2010	Denison	N/A	N/A
8000794	12/2010	Lozano	N/A	N/A
8021299	12/2010	Miesel et al.	N/A	N/A
8027730	12/2010	John	N/A	N/A
8027737	12/2010	Kokones et al.	N/A	N/A
8075499	12/2010	Nathan et al.	N/A	N/A
8109891	12/2011	Kramer et al.	N/A	N/A
8538512	12/2012	Bibian	600/544	A61B 5/04001
2001/0032059	12/2000	Kelly, Jr. et al.	N/A	N/A
2002/0072782	12/2001	Osorio et al.	N/A	N/A
2002/0082480	12/2001	Riff et al.	N/A	N/A
2002/0099417	12/2001	Naritoku et al.	N/A	N/A
2002/0116030	12/2001	Rezai	N/A	N/A
2002/0151939	12/2001	Rezai	N/A	N/A
2002/0188214	12/2001	Misczynski et al.	N/A	N/A
2003/0040680	12/2002	Hassert et al.	N/A	N/A
2003/0074032	12/2002	Gliner	N/A	N/A
2003/0083716	12/2002	Nicolelis et al.	N/A	N/A
2003/0083726	12/2002	Zeijlemaker et al.	N/A	N/A
2003/0125786	12/2002	Gliner et al.	N/A	N/A
2003/0130706	12/2002	Sheffield et al.	N/A	N/A
2003/0144829	12/2002	Geatz et al.	N/A	N/A
2003/0181954	12/2002	Rezai	N/A	N/A
2003/0181958	12/2002	Dobak, III	N/A	N/A
2003/0195588	12/2002	Fischell et al.	N/A	N/A
2003/0208212	12/2002	Cigaina	N/A	N/A
2003/0210147	12/2002	Humbard	N/A	N/A
2003/0212440	12/2002	Boveja	N/A	N/A
2003/0236474	12/2002	Singh	N/A	N/A
2003/0236558	12/2002	Whitehurst et al.	N/A	N/A
2004/0006278	12/2003	Webb et al.	N/A	N/A
2004/0030365	12/2003	Rubin	N/A	N/A

2004/0088024	12/2003	Firlik et al.	N/A	N/A
2004/0111045	12/2003	Sullivan et al.	N/A	N/A
2004/0122484	12/2003	Hatlestad et al.	N/A	N/A
2004/0122485	12/2003	Stahmann et al.	N/A	N/A
2004/0133119	12/2003	Osorio et al.	600/544	N/A
2004/0138516	12/2003	Osorio et al.	N/A	N/A
2004/0138517	12/2003	Osorio et al.	N/A	N/A
2004/0138647	12/2003	Osorio et al.	N/A	N/A
2004/0138711	12/2003	Osorio et al.	N/A	N/A
2004/0153129	12/2003	Pless et al.	N/A	N/A
2004/0158119	12/2003	Osorio et al.	N/A	N/A
2004/0158165	12/2003	Yonce et al.	N/A	N/A
2004/0172085	12/2003	Knudson et al.	N/A	N/A
2004/0172091	12/2003	Rezai	N/A	N/A
2004/0172094	12/2003	Cohen et al.	N/A	N/A
2004/0176812	12/2003	Knudson et al.	N/A	N/A
2004/0176831	12/2003	Gliner et al.	N/A	N/A
2004/0199212	12/2003	Fischell et al.	N/A	N/A
2004/0225335	12/2003	Whitehurst et al.	N/A	N/A
2004/0249302	12/2003	Donoghue et al.	N/A	N/A
2004/0249416	12/2003	Yun et al.	N/A	N/A
2004/0267152	12/2003	Pineda	N/A	N/A
2005/0004621	12/2004	Boveja et al.	N/A	N/A
2005/0020887	12/2004	Goldberg	N/A	N/A
2005/0021092	12/2004	Yun et al.	N/A	N/A
2005/0021103	12/2004	DiLorenzo	N/A	N/A
2005/0021104	12/2004	DiLorenzo	N/A	N/A
2005/0021105	12/2004	Firlik et al.	N/A	N/A
2005/0021106	12/2004	Firlik et al.	N/A	N/A
2005/0021107	12/2004	Firlik et al.	N/A	N/A
2005/0021118	12/2004	Genau et al.	N/A	N/A
2005/0022606	12/2004	Partin et al.	N/A	N/A
2005/0027284	12/2004	Lozano et al.	N/A	N/A
2005/0033378	12/2004	Sheffield et al.	N/A	N/A
2005/0033379	12/2004	Lozano et al.	N/A	N/A
2005/0038484	12/2004	Knudson et al.	N/A	N/A
2005/0049515	12/2004	Misczynski et al.	N/A	N/A
2005/0049655	12/2004	Boveja et al.	N/A	N/A
2005/0060001	12/2004	Singhal et al.	N/A	N/A
2005/0065562	12/2004	Rezai	N/A	N/A
2005/0065573	12/2004	Rezai	N/A	N/A
2005/0065574	12/2004	Rezai	N/A	N/A
2005/0065575	12/2004	Dobak	N/A	N/A
2005/0070971	12/2004	Fowler et al.	N/A	N/A
2005/0075701	12/2004	Shafer	N/A	N/A
2005/0075702	12/2004	Shafer	N/A	N/A
2005/0101873	12/2004	Misczynski et al.	N/A	N/A
2005/0107716	12/2004	Eaton et al.	N/A	N/A
2005/0119703	12/2004	DiLorenzo	N/A	N/A
2005/0124901	12/2004	Misczynski et al.	N/A	N/A

2005/0131467	12/2004	Boveja	N/A	N/A
2005/0131485	12/2004	Knudson et al.	N/A	N/A
2005/0131486	12/2004	Boveja et al.	N/A	N/A
2005/0131493	12/2004	Boveja et al.	N/A	N/A
2005/0143786	12/2004	Boveja	N/A	N/A
2005/0148893	12/2004	Misczynski et al.	N/A	N/A
2005/0148894	12/2004	Misczynski et al.	N/A	N/A
2005/0148895	12/2004	Misczynski et al.	N/A	N/A
2005/0153885	12/2004	Yun et al.	N/A	N/A
2005/0154425	12/2004	Boveja et al.	N/A	N/A
2005/0154426	12/2004	Boveja et al.	N/A	N/A
2005/0165458	12/2004	Boveja et al.	N/A	N/A
2005/0177200	12/2004	George et al.	N/A	N/A
2005/0182389	12/2004	LaPorte et al.	N/A	N/A
2005/0187590	12/2004	Boveja et al.	N/A	N/A
2005/0187796	12/2004	Rosenfeld et al.	N/A	N/A
2005/0192644	12/2004	Boveja et al.	N/A	N/A
2005/0197590	12/2004	Osorio et al.	N/A	N/A
2005/0203366	12/2004	Donoghue et al.	N/A	N/A
2005/0245971	12/2004	Brockway et al.	N/A	N/A
2005/0261542	12/2004	Riehl	N/A	N/A
2005/0277998	12/2004	Tracey et al.	N/A	N/A
2005/0283200	12/2004	Rezai et al.	N/A	N/A
2005/0283201	12/2004	Machado et al.	N/A	N/A
2005/0288600	12/2004	Zhang et al.	N/A	N/A
2005/0288760	12/2004	Machado et al.	N/A	N/A
2006/0009815	12/2005	Boveja et al.	N/A	N/A
2006/0018833	12/2005	Murphy et al.	N/A	N/A
2006/0074450	12/2005	Boveja et al.	N/A	N/A
2006/0079936	12/2005	Boveja et al.	N/A	N/A
2006/0094971	12/2005	Drew	N/A	N/A
2006/0094972	12/2005	Drew	600/523	N/A
2006/0095081	12/2005	Zhou et al.	N/A	N/A
2006/0106430	12/2005	Fowler et al.	N/A	N/A
2006/0111644	12/2005	Guttag et al.	N/A	N/A
2006/0122525	12/2005	Shusterman	N/A	N/A
2006/0122864	12/2005	Gottesman et al.	N/A	N/A
2006/0135877	12/2005	Giftakis et al.	N/A	N/A
2006/0135881	12/2005	Giftakis et al.	N/A	N/A
2006/0149139	12/2005	Bonmassar et al.	N/A	N/A
2006/0155495	12/2005	Osorio et al.	N/A	N/A
2006/0161459	12/2005	Rosenfeld et al.	N/A	N/A
2006/0167497	12/2005	Armstrong et al.	N/A	N/A
2006/0173493	12/2005	Armstrong et al.	N/A	N/A
2006/0173522	12/2005	Osorio	N/A	N/A
2006/0190056	12/2005	Fowler et al.	N/A	N/A
2006/0195163	12/2005	KenKnight et al.	N/A	N/A
2006/0200206	12/2005	Firlik et al.	N/A	N/A
2006/0212091	12/2005	Lozano et al.	N/A	N/A
2006/0212097	12/2005	Varadan et al.	N/A	N/A

2006/0224067	12/2005	Giftakis et al.	N/A	N/A
2006/0224191	12/2005	Dilorenzo	N/A	N/A
2006/0241697	12/2005	Libbus et al.	N/A	N/A
2006/0241725	12/2005	Libbus et al.	N/A	N/A
2006/0293720	12/2005	DiLorenzo	N/A	N/A
2007/0027486	12/2006	Armstrong	N/A	N/A
2007/0027497	12/2006	Parnis	N/A	N/A
2007/0027498	12/2006	Maschino et al.	N/A	N/A
2007/0027500	12/2006	Maschino et al.	N/A	N/A
2007/0032734	12/2006	Najafi et al.	N/A	N/A
2007/0032834	12/2006	Gliner et al.	N/A	N/A
2007/0043392	12/2006	Gliner et al.	N/A	N/A
2007/0055320	12/2006	Weinand	N/A	N/A
2007/0073150	12/2006	Gopalsami et al.	N/A	N/A
2007/0073355	12/2006	Dilorenzo	N/A	N/A
2007/0088403	12/2006	Wyler et al.	N/A	N/A
2007/0088404	12/2006	Wyler et al.	N/A	N/A
2007/0100278	12/2006	Frei et al.	N/A	N/A
2007/0100392	12/2006	Maschino et al.	N/A	N/A
2007/0142862	12/2006	Dilorenzo	N/A	N/A
2007/0142873	12/2006	Esteller et al.	N/A	N/A
2007/0149952	12/2006	Bland et al.	N/A	N/A
2007/0150024	12/2006	Leyde et al.	N/A	N/A
2007/0150025	12/2006	Dilorenzo et al.	N/A	N/A
2007/0156450	12/2006	Roehm et al.	N/A	N/A
2007/0161919	12/2006	DiLorenzo	N/A	N/A
2007/0162086	12/2006	DiLorenzo	N/A	N/A
2007/0167991	12/2006	DiLorenzo	N/A	N/A
2007/0173901	12/2006	Reeve	N/A	N/A
2007/0173902	12/2006	Maschino et al.	N/A	N/A
2007/0179534	12/2006	Firlik et al.	N/A	N/A
2007/0179557	12/2006	Maschino et al.	N/A	N/A
2007/0179558	12/2006	Gliner et al.	N/A	N/A
2007/0208212	12/2006	DiLorenzo	N/A	N/A
2007/0213785	12/2006	Osorio et al.	N/A	N/A
2007/0233192	12/2006	Craig	N/A	N/A
2007/0239210	12/2006	Libbus et al.	N/A	N/A
2007/0242661	12/2006	Tran	N/A	N/A
2007/0244407	12/2006	Osorio	N/A	N/A
2007/0249953	12/2006	Frei et al.	N/A	N/A
2007/0249954	12/2006	Virag et al.	N/A	N/A
2007/0255147	12/2006	Drew et al.	N/A	N/A
2007/0255155	12/2006	Drew et al.	N/A	N/A
2007/0260147	12/2006	Giftakis et al.	N/A	N/A
2007/0260289	12/2006	Giftakis et al.	N/A	N/A
2007/0265536	12/2006	Giftakis et al.	N/A	N/A
2007/0272260	12/2006	Nikitin et al.	N/A	N/A
2007/0282177	12/2006	Pilz	N/A	N/A
2007/0287931	12/2006	Dilorenzo	N/A	N/A
2008/0004904	12/2007	Tran	N/A	N/A

2008/0021341	12/2007	Harris et al.	N/A	N/A
2008/0027347	12/2007	Harris et al.	N/A	N/A
2008/0027348	12/2007	Harris et al.	N/A	N/A
2008/0027515	12/2007	Harris et al.	N/A	N/A
2008/0033502	12/2007	Harris et al.	N/A	N/A
2008/0033503	12/2007	Fowler et al.	N/A	N/A
2008/0033508	12/2007	Frei et al.	N/A	N/A
2008/0046035	12/2007	Fowler et al.	N/A	N/A
2008/0064934	12/2007	Frei et al.	N/A	N/A
2008/0071185	12/2007	Beck	600/529	A61B 5/0816
2008/0071323	12/2007	Lowry et al.	N/A	N/A
2008/0077028	12/2007	Schaldach et al.	N/A	N/A
2008/0081958	12/2007	Denison et al.	N/A	N/A
2008/0103548	12/2007	Fowler et al.	N/A	N/A
2008/0114417	12/2007	Leyde	N/A	N/A
2008/0119900	12/2007	DiLorenzo	N/A	N/A
2008/0125820	12/2007	Stahmann et al.	N/A	N/A
2008/0139870	12/2007	Gliner et al.	N/A	N/A
2008/0146890	12/2007	LeBoeuf et al.	N/A	N/A
2008/0146959	12/2007	Sheffield et al.	N/A	N/A
2008/0161712	12/2007	Leyde	N/A	N/A
2008/0161713	12/2007	Leyde et al.	N/A	N/A
2008/0161879	12/2007	Firlik et al.	N/A	N/A
2008/0161880	12/2007	Firlik et al.	N/A	N/A
2008/0161881	12/2007	Firlik et al.	N/A	N/A
2008/0161882	12/2007	Firlik et al.	N/A	N/A
2008/0183096	12/2007	Snyder et al.	N/A	N/A
2008/0183097	12/2007	Leyde et al.	N/A	N/A
2008/0208013	12/2007	Zhang et al.	N/A	N/A
2008/0208074	12/2007	Snyder et al.	N/A	N/A
2008/0208284	12/2007	Rezai et al.	N/A	N/A
2008/0208781	12/2007	Snyder	N/A	N/A
2008/0234598	12/2007	Snyder et al.	N/A	N/A
2008/0255582	12/2007	Harris	N/A	N/A
2008/0258907	12/2007	Kalpaxis	N/A	N/A
2008/0269579	12/2007	Schiebler	N/A	N/A
2008/0275327	12/2007	Faarbaek et al.	N/A	N/A
2008/0275328	12/2007	Jones	N/A	N/A
2008/0275349	12/2007	Halperin et al.	N/A	N/A
2008/0281376	12/2007	Gerber et al.	N/A	N/A
2008/0281381	12/2007	Gerber et al.	N/A	N/A
2008/0281550	12/2007	Hogle et al.	N/A	N/A
2008/0319281	12/2007	Aarts	N/A	N/A
2009/0030345	12/2008	Bonnet et al.	N/A	N/A
2009/0040052	12/2008	Cameron et al.	N/A	N/A
2009/0054737	12/2008	Magar et al.	N/A	N/A
2009/0054742	12/2008	Kaminska et al.	N/A	N/A
2009/0054795	12/2008	Misczynski et al.	N/A	N/A
2009/0060287	12/2008	Hyde et al.	N/A	N/A
2009/0062696	12/2008	Nathan	600/595	A61B 5/4082

2009/0076350	12/2008	Bly et al.	N/A	N/A
2009/0099624	12/2008	Kokones et al.	N/A	N/A
2009/0099627	12/2008	Molnar et al.	N/A	N/A
2009/0105785	12/2008	Wei et al.	N/A	N/A
2009/0124923	12/2008	Sackellares	600/544	A61B 5/048
2009/0137921	12/2008	Kramer et al.	N/A	N/A
2009/0227882	12/2008	Foo	N/A	N/A
2009/0227888	12/2008	Salmi et al.	N/A	N/A
2009/0322540	12/2008	Richardson et al.	N/A	N/A
2010/0010382	12/2009	Panken	N/A	N/A
2010/0010392	12/2009	Skelton et al.	N/A	N/A
2010/0010583	12/2009	Panken et al.	N/A	N/A
2010/0023348	12/2009	Hardee et al.	N/A	N/A
2010/0056878	12/2009	Partin et al.	N/A	N/A
2010/0106217	12/2009	Colborn	N/A	N/A
2010/0109875	12/2009	Ayon et al.	N/A	N/A
2010/0121214	12/2009	Giftakis et al.	N/A	N/A
2010/0217533	12/2009	Nadkarni et al.	N/A	N/A
2010/0223020	12/2009	Goetz	N/A	N/A
2010/0228103	12/2009	Schecter	N/A	N/A
2010/0228314	12/2009	Goetz	N/A	N/A
2010/0268056	12/2009	Picard et al.	N/A	N/A
2010/0274303	12/2009	Bukham	N/A	N/A
2010/0280336	12/2009	Giftakis et al.	N/A	N/A
2010/0280578	12/2009	Skelton et al.	N/A	N/A
2010/0280579	12/2009	Denison et al.	N/A	N/A
2010/0286567	12/2009	Wolfe et al.	N/A	N/A
2010/0298661	12/2009	McCombie et al.	N/A	N/A
2010/0298742	12/2009	Perlman et al.	N/A	N/A
2010/0305665	12/2009	Miesel et al.	N/A	N/A
2010/0312188	12/2009	Robertson et al.	N/A	N/A
2011/0029044	12/2010	Hyde et al.	N/A	N/A
2011/0040204	12/2010	Ivorra et al.	N/A	N/A
2011/0040546	12/2010	Gerber et al.	N/A	N/A
2011/0060252	12/2010	Simonsen et al.	N/A	N/A
2011/0066062	12/2010	Banet et al.	N/A	N/A
2011/0066081	12/2010	Goto	N/A	N/A
2011/0137372	12/2010	Makous et al.	N/A	N/A
2011/0172545	12/2010	Grudic et al.	N/A	N/A
2011/0230730	12/2010	Quigg et al.	N/A	N/A
2011/0245629	12/2010	Giftakis et al.	N/A	N/A
2011/0251468	12/2010	Osorio	N/A	N/A
2011/0251469	12/2010	Varadan	N/A	N/A
2011/0270117	12/2010	Warwick et al.	N/A	N/A
2011/0270134	12/2010	Skelton	N/A	N/A
2011/0295127	12/2010	Sandler et al.	N/A	N/A
2011/0306845	12/2010	Osorio	N/A	N/A
2011/0306846	12/2010	Osorio	N/A	N/A
2011/0313484	12/2010	Hincapie Ordonez et al.	N/A	N/A

FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
0944411	12/2000	EP	N/A
1486232	12/2003	EP	N/A
0064336	12/1999	WO	N/A
2004036377	12/2003	WO	N/A
2005067599	12/2004	WO	N/A
2006050144	12/2005	WO	N/A
2006122148	12/2005	WO	N/A
2007066343	12/2006	WO	N/A
2007142523	12/2006	WO	N/A
2008054580	12/2007	WO	N/A

OTHER PUBLICATIONS

Osorio, I. et al., "Toward a Quantitative Multivariate Analysis of the Efficacy of Antiseizure Therapies," Epilepsy & Behavior, Academic Press, San Diego, CA., vol. 18, No. 4, Aug. 1, 2010, pp. 335-343. cited by applicant

PCT Search Report and Written Opinion for International Application No. PCT/US2012/027639, dated Oct. 4, 2012, 22 pages. cited by applicant

Bachman, D. et al., "Effects of Vagal Volleys and Serotonin on Units of Cingulate Cortex in Monkeys", Brain Research, vol. 130, 1977, pp. 253-269. cited by applicant

Baevskii, R., "Analysis of Heart Rate Variability in Space Medicine", Human Physiology, vol. 28, No. 2, 2002, pp. 202-213. cited by applicant

Baevsky, R., "Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station", Journal of Applied Physiological, vol. 103, 2007, pp. 156-161. cited by applicant

Boon, P. et al., "Programmed and Magnet-Induced Vagus Nerve Stimulation for Refractory Epilepsy", Journal of Clinical Neurophysiology, vol. 18, No. 5, 2001, p. 402-407. cited by applicant

Boon, P. et al., "Vagus Nerve Stimulation for Epilepsy, Clinical Efficacy of Programmed and Magnet Stimulation", Acta Neurochirurgica Supplement, vol. 79, 2002, pp. 93-98. cited by applicant

Borovikova, L. et al., "Vagus Nerve Stimulation Attenuates the Systemic Inflammatory Response to Endotoxin", Letters to Nature, vol. 405, May 2000, pp. 458-462. cited by applicant

Brack, K. et al., "Interaction Between Direct Sympathetic and Vagus Nerve Stimulation on Heart Rate in the Isolated Rabbit Heart", Experimental Physiology, vol. 89, No. 1, 2004, pp. 128-139. cited by applicant

Chakravarthy, N. et al., "Controlling Synchronization in a Neuron-Level Population Model", International Journal of Neural Systems, vol. 17, No. 2, 2007, pp. 123-138. cited by applicant

Clark, K. et al., "Posttraining Electrical Stimulation of Vagal Afferents with Concomitant Vagal Efferent Inactivation Enhances Memory Storage Processes in the Rat", Neurobiology of Learning and Memory, vol. 70, Article No. NL983863, 1998, pp. 364-373. cited by applicant

Frei, M. et al., "Left Vagus Nerve Stimulation with the Neurocybernetic Prosthesis has Complex Effects on Heart Rate and on its Variability in Humans", Epilepsia, vol. 42, No. 8, 2001, pp. 1007-1016. cited by applicant

George, M. et al., "Vagus Nerve Stimulation: A New Tool for Brain Research and Therapy", Society of Biological Psychiatry, vol. 47, 2000, pp. 287-295. cited by applicant

Hallowitz, R. et al., "Effects of Vagal Volleys on Units of Intralaminar and Juxtalaminar Thalamic

Nuclei in Monkeys", Brain Research, vol. 130, No. 2, Jul. 1977, pp. 271-286. cited by applicant

Henry, T., "Therapeutic Mechanisms of Vague Name Stimulation", Neurology, vol. 59 (Supp. 4), Sep. 2002, pp. S3-S14. cited by applicant

Iasemidis, L. et al., "Dynamical Resetting of the Human Brain at Epileptic: Application of Nonlinear Dynamics and Global Optimization Techniques", IEEE Transactions on Biomedical Engineering, vol. 51, No. 3, Mar. 2004, pp. 493-508. cited by applicant

Iasemidis, L. et al., "Spatiotemporal Transition to Epileptic Seizures: A Nonlinear Dynamical Analysis of Scalp and Intracranial EEG Recordings", Spatiotemporal Models in Biological and Artificial Systems, IOS Press, 1997, pp. 81-88. cited by applicant

Iasemidis, L., "Epileptic Seizure Prediction and Control", IEEE Transactions on Biomedical Engineering, vol. 50, No. 5, May 2003, pp. 549-558. cited by applicant

Kautzner, J. et al., "Utility of Short-Term Heart Rate Variability for Prediction of Sudden Cardiac Death After Acute Myocardial Infarction", Acta Univ Palacki Olomuc Fac Med., vol. 141, 1998, pp. 69-73. cited by applicant

Koenig, S. et al., "Vagus Nerve Stimulation Improves Severely Impaired Heart Rate Variability in a Patient with Lennox-Gastaut-Syndrome", Seizure, vol. 17, Issue 5, Jul. 2008, pp. 469-472. cited by applicant

Koo, B., "EEG Changes with Vagus Nerve Stimulation", Journal of Clinical Neurophysiology, vol. 18, No. 5, Sep. 2001, pp. 434-441. cited by applicant

Krittayaphong, M. et al., "Heart Rate Variability in Patients with Coronary Artery Disease: Differences in Patients with Higher and Lower Depression Scores", Psychosomatic Medicine, vol. 59, 1997, pp. 231-235. cited by applicant

Leutmezer, F. et al., "Electrocardiogramges at the Onset of Epileptic Seizures", Epilepsia, vol. 44, No. 3, 2003, pp. 348-354. cited by applicant

Lewis, M. et al., "Vagus Nerve Stimulation Decreases Left Ventricular Contractility in Vivo in the Human and Pig Heart", The Journal of Physiology, vol. 534, No. 2, 2001, pp. 547-552. cited by applicant

Li, M. et al., "Vagal Nerve Stimulation Markedly Improves Long-Term Survival After Chronic Heart Failure in Rats", Circulation, Jan. 2004, vol. 109, No. 1, pp. 120-124. cited by applicant

Licht, C., "Association Between Major Depressive Disorder and Heart Rate Variability in the Netherlands Study of Depression and Anxiety (NESDA)", Arch. Gen. Psychiatry, vol. 65, No. 12, Dec. 2008, pp. 1358-1367. cited by applicant

Lockard, J. et al., "Feasibility and safety of vagal stimulation in monkey model", Epilepsia, vol. 31 (Supp. 2), 1990, pp. S20-S26. cited by applicant

Long, T. et al., "Effectiveness of Heart Rate Seizure Detection Compared to EEG in an Epilepsy Monitoring Unit (EMU)", Abstract of AES Proceedings, Epilepsia, vol. 40, Supplement 7, 1999, p. 174. cited by applicant

McClintock, P., "Can Noise Actually Boost Brain Power", Physics World, Jul. 2002, vol. 15, pp. 20-21. cited by applicant

Mori, T. et al., "Noise-Induced Entrainment and Stochastic Resonance in Human Brain Waves", Physical Review Letters, vol. 88, No. 21, 2002, pp. 218101-1-2180101-4. cited by applicant

Mormann, F. et al., "Seizure Prediction: The Long and Winding Road", Brain, vol. 130, 2007, pp. 314-333. cited by applicant

Nouri, M., "Epilepsy and the Autonomic Nervous System", emedicine, Updated May 5, 2006, http://www.emedicine.com/neuro/toplo658.htm, pp. 1-14. cited by applicant

O'Donovan, C. et al., "Computerized Seizure Detection Based on Heart Rate Changes", Abstract of AES Proceedings, Epilepsia, vol. 36, Supplement 4, 1995, p. 7. cited by applicant

O'Regan, M. et al., "Abnormalities in Cardiac and Respiratory Function Observed During Seizures in Childhood", Developmental Medicine & Child Neurology, vol. 47, 2005, pp. 4-9. cited by applicant

Pathwardhan, R. et al., "Control of Refractory Status Epilepticus Precipitated by Anticonvulsant Withdrawal Using Vagal Nerve Stimulation: A Case Report", Surgical Neurology, Issue 64, Aug. 2005, pp. 170-173. cited by applicant

PCT Search Report and Written Opinion for International application No. PCT/US2011/054287 dated Mar. 12, 2012, 18 pages. cited by applicant

Rugg-Gunn, F. et al., "Cardiac Arrhythmias in Focal Epilepsy: a Prospective Long-Term Study", Lancet, vol. 364, Dec. 2004, pp. 2212-2219. cited by applicant

Schernthaner, C. et al., "Autonomic Epilepsy—The Influence of Epileptic Discharges on Heart Rate and Rhythm", The Middle European Journal of Medicine, vol. 111, No. 10, 1999, pp. 392-401. cited by applicant

Terry, R. et al., "The Implantable Neurocybernetic Prosthesis System", Pacing and Clinical Electrophysiology, vol. 14, No. 1, Jan. 1991, pp. 86-93. cited by applicant

Tubbs, R. et al., "Left-Sided Vagus Nerve Stimulation Decreases Intracranial Pressure Without Resultant Bradycardia in the Pig: A Potential Therapeutic Modality for Humans", Child's Nervous System, vol. 20, No. 5, May 2004, pp. 309-312. cited by applicant

Vonck, K. et al., "The Mechanism of Action of Vagus Nerve Stimulation for Refractory Epilepsy—The Current Status", Journal of Neurophysiology, vol. 18, No. 5, 2001, pp. 394-401. cited by applicant

Woodbury, J. et al., "Vagal stimulation reduces the severity of maximal electroshock seizures in intact rats: use of a cuff electrode for stimulating and recording", Pacing and Clinical Electrophysiology, vol. 14, Jan. 1991, pp. 94-107. cited by applicant

Zabara, J. et al., "Neuroinhibition in the regulation of emesis", Space Life Sciences, vol. 3, Issue 3, Jun. 1972, pp. 282-292. cited by applicant

Zabara, J., "Inhibition of Experimental Seizures in Canines by Repetitive Vagal Stimulation", Epilepsia, vol. 33, No. 6, 1992, pp. 1005-1012. cited by applicant

Zabara, J., "Neural Control of Circulation I", The Physiologist, vol. 28, No. 4, Aug. 1985, pp. 273-277. cited by applicant

Zabara, J., "Neuroinhibition of Xylaine Induced Emesis", Pharmacology & Toxicology, vol. 63, Aug. 1988, pp. 70-74. cited by applicant

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Background/Summary

(1) This application is a continuation-in-part of prior co-pending U.S. patent application Ser. No. 13/040,996, filed Mar. 4, 2011, which is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

(1) This invention relates generally to medical device systems and, more particularly, to medical device systems and methods capable of assessing and managing extreme events related to seizures, e.g., seizures resulting from epilepsy.

DESCRIPTION OF THE RELATED ART

(2) Generalized tonic-clonic status epilepticus, referred to herein as Convulsive Status Epilepticus (CSE) is a neurological emergency with an estimated incidence of about 20 out of 100,000 patients and is generally considered an extreme event. CSE is also associated with a mortality rate between

3% and 40% depending on etiology, age, status type, and status duration. CSE, in particular, requires immediate, aggressive, and effective treatment to stop seizure activity, to prevent neuronal damage, systemic complications and the possibility of death. Most investigations on prognosis of status epilepticus (SE) have focused on mortality, and some research suggests that outcome basically depends on the etiological and biological background but also that the earlier the therapeutic intervention the higher the probability of controlling it. Additionally, non-convulsive status epilepticus (nCSE), while not a medical emergency of the magnitude of CSE, it is also an extreme event as nevertheless it increases the risk of bodily injury and neurologic deficits such as permanent potentially severe impairment in memory.

(3) CSE and nCSE are defined based on the duration of a single seizure and its variations or on the lack of recovery of certain neurologic functions to their inter-ictal (baseline) levels in the context of closely spaced seizures. The focus on seizure duration or frequency or on level of consciousness or of awareness to determine if a patient is in status epilepticus has important limitations, since signals or indices from others systems such as cardio-vascular, respiratory, endocrine and metabolic which are also adversely impacted by the seizures and which directly contribute to the increased (compared to the non-epileptic population) morbidity and mortality of patients with epilepsy are disregarded. The state of the art views and treats Status Epilepticus narrowly and ineffectively. Embodiments of this invention takes a system's approach by quantifying the impact of seizures on bodily functions (e.g., neurologic, cardiovascular) to determine the probability they are harbinger of extreme events (e.g., status epilepticus) and to prevent them from occurring, or if they are extreme, to provide early treatment and/or warning to avert serious neurological and medical sequelae or even fatal outcomes.

(4) Sudden Unexpected Death in Epilepsy, or "SUDEP," another extreme event, is a phenomenon in which a patent with epilepsy dies unexpectedly and without an apparent, outstanding cause, that is, the death is unexplained since autopsy results are unrevealing. One of the main risk factors for SUDEP is the lack of seizure control with first line drugs prescribed alone or in any safe combination and dosage. Whether or not the first in a chain of ultimately fatal events leading to SUDEP is a seizure, the defining event is likely to be either cardiac (e.g., ventricular fibrillation or asystole) or respiratory (e.g., apnea) or both. Currently, the monitoring, detection, prediction and prevention of SUDEP are underdeveloped and markedly limited in breadth and depth of scope, limitations which embodiments of this invention address.

(5) CSE and nCSE alter autonomic nervous system function and SUDEP may be caused by autonomic dysfunction. Since brain/neurological activity such as electrical activity, whether normal or abnormal, and autonomic functions (e.g., cardiovascular activity, respiration, etc.), referred to herein as body signals (from which body data may be derived), are functionally tightly coupled; monitoring these body signal provides valuable information. This is the first invention to utilize not only neurologic, autonomic, metabolic, endocrine and tissue stress marker signals but do so in a multi-variant adaptive manner to optimize sensitivity and specificity of detection of extreme epileptic events (e.g., CSE, SUDEP), and, more importantly to anticipate them.

SUMMARY OF EMBODIMENTS

(6) In one aspect of the present invention, a non-transitive, computer readable program storage device encoded with instructions that, when executed by a computer, performs a method for identifying an extreme seizure event in a patient, is provided. The method includes identifying at least two seizure events; determining at least one inter-seizure interval (ISI) value related to the at least two seizure events; comparing the determined at least one ISI value to at least one reference value; and identifying an occurrence of an extreme seizure event, based upon the comparison of the determined ISI value to the at least one reference value.

(7) In another aspect of the present invention, a method for identifying an extreme seizure event in a patient is provided. The method includes detecting a first seizure event; determining at least one body index affected by the first seizure event. The body index comprises at least one of an

autonomic index, a neurologic index, a metabolic index, an endocrine index, a tissue stress index, a physical fitness/body integrity index, or a quality of life index. The indices are based upon body data. The at least one body index has at least a first body index reference value associated with an inter-ictal state. The method also comprises detecting a second seizure event and identifying an occurrence of an extreme seizure event based at least in part in response to a determination that the second seizure event occurred prior to the determined at least one body index value affected by the first seizure event returning to the first body index reference value.

(8) In yet another aspect of the present invention, a non-transitive, computer readable program storage device encoded with instructions that, when executed by a computer, performs another method for identifying an extreme seizure event in a patient, is provided. The method includes identifying a first seizure event of a first type and a second seizure event of the first type; identifying a third seizure event of a second type and a fourth seizure event of the second type; determining a first inter-seizure interval (ISI) value between the first and the second seizures; determining a second inter-seizure interval (ISI) value between the third and fourth seizures; performing a first comparison of the determined first ISI value to at least a first reference value; performing a second comparison of the determined second ISI value to at least a second reference value; and identifying an occurrence of an extreme seizure event, based upon at least the first or the second comparisons.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) The present invention may be understood by reference to the following description taken in conjunction with the accompanying drawings, in which like reference numerals identify like elements, and in which:

(2) FIG. **1**A provides an exemplary stylized diagram of a medical device which may be implanted into a patient's body for providing a therapeutic electrical signal to a neural structure of the patient's body, in accordance with one illustrative embodiment of the present invention;

(3) FIG. **1**B provides an exemplary stylized diagram of a medical device which may be implanted into a patient's body for providing a therapeutic electrical signal to a neural structure of the patient's body, in accordance with one illustrative embodiment of the present invention;

(4) FIG. **1**C provides a stylized diagram of an exemplary medical device which may be implanted into a patient's body for providing a therapeutic electrical signal to a neural structure of the patient's body, in accordance with one illustrative embodiment of the present invention;

(5) FIG. **2** illustrates an exemplary medical device for anticipating, detecting, assessing and managing (e.g., treating, warning, logging) extreme events related to epilepsy, in accordance with an illustrative embodiment of the present invention;

(6) FIG. **3** provides a stylized diagram of an exemplary medical device and its different data acquisition units that may be implanted into a patient's body, in accordance with one illustrative embodiment of the present invention;

(7) FIG. **4** provides a stylized diagram of an exemplary medical device which may be implanted into a patient's body, in accordance with one illustrative embodiment of the present invention;

(8) FIG. **5**A provides a stylized diagram of a seizure severity index unit for determining a seizure severity index using body data and seizure data, in accordance with one illustrative embodiment of the present invention;

(9) FIG. **5**B provides a stylized diagram of a patient impact unit for determining a patient impact using body data and seizure data, in accordance with one illustrative embodiment of the present invention;

(10) FIG. **5**C provides a stylized diagram of an inter-seizure interval index unit for determining a

time elapsed between the onset of consecutive or non-consecutive seizures using body data, in accordance with one illustrative embodiment of the present invention;

(11) FIG. **6** provides a stylized diagram of a warning unit for warning of a patient's proclivity towards an extreme epileptic event/state or of its occurrence, in accordance with one illustrative embodiment of the present invention;

(12) FIG. **7** provides a flowchart depiction of a method for identifying and/or managing an extreme epileptic event/state, in accordance with one illustrative embodiment of the present invention;

(13) FIG. **8** provides a flowchart depiction of a method implementing responsive actions (warning, treatment, data logging among others) in response to determining that an extreme epileptic event/state is probable, is occurring or has occurred, in accordance with one illustrative embodiment of the present invention;

(14) FIG. **9** provides a flowchart depiction of a method for warning and/or providing a treatment to a patient likely to be in, or to recently have been in an extreme epileptic event/state, in accordance with one illustrative embodiment of the present invention;

(15) FIG. **10** illustrates a stylized diagram for determining and executing a treatment plan by a healthcare provider, caregiver and/or patient subsequent to overriding automated treatment an extreme epileptic event/state, in accordance with one illustrative embodiment of the present invention;

(16) FIG. **11** provides a stylized diagram of a seizure impact ranking unit adapted to quantify seizure impact based on its effects (type, magnitude and duration) on neurologic, autonomic, metabolic, endocrine, and/or physical integrity (e.g., damage to musculoskeletal system), tissue stress markers and/or time spent in seizure per unit time using body data, in accordance with one illustrative embodiment of the present invention;

(17) FIG. **12** provides a flowchart depiction of a method for identifying and/or managing a an extreme epileptic event/state, in accordance with one illustrative embodiment of the present invention;

(18) FIG. **13** provides a graphical representation of the probability density function of seizure energy estimated from subjects with pharmaco-resistant seizures, in accordance with one illustrative embodiment;

(19) FIG. **14**A provides a graphical representation one exemplary probability density function of inter-seizure intervals in patients with pharmaco-resistant epilepsies, in accordance with one illustrative embodiment;

(20) FIG. **14**B provides a graphical depiction of ictal, inter-ictal/inter-seizure, post-ictal and inter-ictal periods, in accordance with one illustrative embodiment;

(21) FIG. **15** provides a graphical representation of an increase in seizure likelihood (y-axis) over baseline as a function of time before and after a seizure as determined in a pooled group of patients, according to one illustrative embodiment;

(22) FIG. **16**A graphically depicts changes in responsiveness/awareness and recovery to baseline as a function of seizure severity in a case on non-extreme events, in accordance with one illustrative embodiment;

(23) FIG. **16**B depicts an example of an extreme epileptic state where responsiveness/awareness does not recover to baseline in-between seizures due to their severity, in accordance with one illustrative embodiment;

(24) FIG. **16**C depicts an example of changes in responsiveness/awareness as a function of inter-seizure interval in a non-extreme event case, in accordance with one illustrative embodiment;

(25) FIG. **16**D depicts an illustrative example of changes in responsiveness/awareness associated with short inter-seizure intervals and compatible with an extreme epileptic event/state as responsiveness remains below baseline;

(26) FIG. **17**A provides a graphical representation of a seizure measure(s) and/or dimension(s) with more than one threshold (bottom panel), and where said thresholds may be above or below a

reference threshold, in accordance with one illustrative embodiment;

(27) FIG. **17**B depicts that in patients with pharmaco-resistant seizures, the longer the time elapsed from the last seizure, the longer the time until the next seizure, in accordance with one or more embodiments;

(28) FIG. **18** provides a stylized diagram of impact of status epilepticus on body organ functions, seizures and quality of life;

(29) FIG. **19** provides a stylized depiction of distributions (in percentiles) of values of an exemplary body index chart, during the inter-ictal, ictal and postictal periods, in accordance with one embodiment;

(30) FIG. **20** provides a stylized depiction of an exemplary body index chart, including an outlier (e.g., it exceeds the 95.sup.th percentile of ictal values) body index value, in accordance with one embodiment;

(31) FIG. **21** provides a stylized depiction of the possible distribution (in percentiles) of an exemplary body signal energy chart including an outlier (e.g., the drop in energy exceeds the 5.sup.th percentile of postictal values), in accordance with one embodiment; and

(32) FIG. **22** provides a stylized depiction of various time periods within distributions (in percentiles) of values of an exemplary body index chart, during the inter-ictal, ictal and post-ictal periods, in accordance with one embodiment.

(33) While the invention is susceptible to various modifications and alternative forms, specific embodiments thereof have been shown by way of example in the drawings and are herein described in detail. It should be understood, however, that the description herein of specific embodiments is not intended to limit the invention to the particular forms disclosed, but on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention as defined by the appended claims.

DETAILED DESCRIPTION OF EMBODIMENTS

(34) Illustrative embodiments of the invention are described herein. In the interest of clarity, not all features of an actual implementation are described in this specification. In the development of any such actual embodiment, numerous implementation-specific decisions must be made to achieve the design-specific goals, which will vary from one implementation to another. It will be appreciated that such a development effort, while possibly complex and time-consuming, would nevertheless be a routine undertaking for persons of ordinary skill in the art having the benefit of this disclosure.

(35) This document does not intend to distinguish between components that differ in name but not function. In the following discussion and in the claims, the terms "including" and "includes" are used in an open-ended fashion, and thus should be interpreted to mean "including, but not limited to." Also, the term "couple" or "couples" is intended to mean either a direct or an indirect electrical connection. "Direct contact," "direct attachment," or providing a "direct coupling" indicates that a surface of a first element contacts the surface of a second element with no substantial attenuating medium there between. The presence of small quantities of substances, such as bodily fluids, that do not substantially attenuate electrical connections does not vitiate direct contact. The word "or" is used in the inclusive sense (i.e., "and/or") unless a specific use to the contrary is explicitly stated. The terms "adapted to" and "capable of" as used herein may imply, among other things, that a device has a structure sufficient to perform some task or operation. The terms "adapted to" and "capable of" are not used to state (implicitly or explicitly) mere intended use limitations in the description and claims of the instant Application.

(36) The term "electrode" or "electrodes" described herein may refer to one or more stimulation electrodes (i.e., electrodes for delivering a therapeutic signal generated by an MD to a tissue), sensing electrodes (i.e., electrodes for sensing a physiological indication of a patient's body), and/or electrodes that are capable of delivering a therapeutic signal, as well as performing a sensing function.

(37) The terms "specific care" described herein may be care provided to a patient that is targeted at

a seizure event itself such as electrical stimulation, anti-seizure drug treatments, and the like. The term "supportive care" described herein is care targeted to maintain vital functions within the normal range and minimizing the risk of tissue damage through body/brain cooling, administration of medications with antioxidant properties and/or the like.

(38) The term "occurrence" used in reference to epileptic events may mean a risk of occurrence, an increased/increasing risk of occurrence, or an actual occurrence of such events. The terms "seizure event" and "epileptic event" may be used interchangeably.

(39) The terms "microscopic," "mesoscopic," and "macroscopic" described herein may show time periods which may be used in observation of seizure events and/or extreme seizure events, body changes such as heart wave and heart wave complex morphology, heart rate variability, and/or other body data described herein. "Microscopic" may correspond to the scale of observation of at least part of a heart beat such as that represented by an EKG's P-QRS-T complex or may correspond to a period of time that is less than a "mesoscopic" time period (e.g., less than 10 seconds). "Mesoscopic" may correspond to a scale of observation of several seconds to tens of seconds (e.g., 10-300 seconds) to capture at least in part, a change in the shape of heart rate plot representative of a state change. "Macroscopic" may correspond to a scale of observation longer than 300 seconds that may be used to encompass more than the information contained in the "mesoscopic" scale or window as described above. In the context of the description provided herein, the term "window" may be used to refer to one or more of the "mesoscopic," "microscopic" and "macroscopic" time periods described above.

(40) A patient may experience certain types of seizures which may be classified as "extreme" As defined herein, extreme seizures may be classified based on: a) certain metrics such as a seizure severity index (SSI), inter-seizure interval (ISI), post-ictal severity index (PISI) and/or b) the impact the seizures have on a subject, which in some embodiments may be determined using the metrics listed herein (see, e.g., a) above), and in other embodiments may be influenced by additional measures, such as the effects of a fall or other injuries associated with a particular seizure event.

(41) Extreme epileptic/seizure events may be classified using the various metrics described herein. In one embodiment, an extreme epileptic/seizure event may be classified at least as one of a generalized seizure or a partial seizure. The term "partial seizure" may encompass complex partial seizures and/or simple partial seizure. Both generalized seizures and partial seizures may result in and/or become extreme epileptic events based on one or more of the criteria described herein. For example, a generalized seizure may result in a seizure severity index (such as heart rate, discussed in further detail below) change being outside a reference range for SSI. The increase in magnitude of the variables that are indicative of an increase in the severity of seizure may lead to a generalized seizure extreme epileptic event. This event may be quantifiable by comparing the SSI to a predetermined reference threshold.

(42) A patient's seizures may be classified as "non-extreme" or as "extreme". As defined herein, "extreme" seizures events may be classified based on certain metrics such as a seizure intensity, duration or extent of spread, seizure severity, inter-seizure interval duration and/or the impact or burden the extreme seizures have on a subject (which may be dependent or independent of intensity, duration, extent of spread, seizure severity, or inter-seizure interval duration), also called the patient seizure impact (PSimp). Extreme events may be defined quantitatively or qualitatively. Quantitatively, as defined herein, they correspond for example to those to the far right (on the x-axis) of a seizure severity probability density function, or in the case of a normal/normalized distribution of seizure severity to those more than one standard deviation beyond the mean, or as above (e.g., 80.sup.th) or also as those whose conditional probability of occurrence is very low. In the case of inter-seizure intervals (ISIs), extreme events are defined quantitatively as those to the far left on an ISI probability density function, or in the case of a normal/normalized distribution, as those more than one standard deviation below the mean, or as below the 20.sup.th percentile of an

ISI distribution. Qualitatively, extreme events as defined herein, are those whose severity (e.g. intensity, duration, etc.), frequency or impact on body organs/systems (reversible or irreversible) among others, exceeds expected and commonly observed outcomes. For example, a patient with long history of convulsions, may develop pulmonary edema after one of these seizures. The fact that its impact (pulmonary edema) is both serious and rare/unprecedented makes this seizure "extreme". It should be noticed that for an epileptic event to qualify as extreme it need not only be severe or rare.

(43) A patient may have other certain kinds of seizure events which may be classified as "extreme." Seizure events such as status epilepticus (or increased risk thereof), risk of death, seizure events of a certain energy, severity and/or occurring within certain time intervals, seizures with certain effects (e.g., falls, cardiac and/or respiratory dysfunction, cardiac and/or respiratory distress, etc), and/or the like, may all be considered extreme seizure events for certain patients. Classifying a seizure event as "extreme" may be based upon an impact upon (or seriousness in relation to) the patient's health and well-being or the condition of the patient's disease state (e.g., a patient's epileptic disease state), or such a classification may be made in some cases based upon characteristics of the seizure event. In different cases, extreme seizure events may be classified according to other standards as well, and need not necessarily be specifically limited to those described herein. Similarly, extreme seizure events may be a combination of the above described classifications. An extreme seizure event (e.g., status epilepticus or risk of status epilepticus) may result in a pathophysiological effect in a patient such as, but not limited to, damage to brain tissue resulting in permanent and/or serious impairment of motor, visual, sensory and/or cognitive skills, respiratory failure, cardiac failure, pulmonary edema, cardiac arrhythmia, metabolic acidosis, liver and/or renal failure, bed sores, bone fractures, abrasions, bruises, organ or multi-organ failure, arterial hypertension, tissue hypoxia and/or tissue hypercarbia or death.

(44) As defined herein, "extreme seizures" may be classified based on certain metrics such as, for example, a seizure severity index (SSI) and/or on the impact a seizure has on a subject, i.e., the patient impact (PSimp) or patient seizure burden. Seizure metrics may be: a) peak energy (defined for example as the product of peak intensity and duration); b) severity (defined for example as the sum of peak energies at each brain site engaged in seizure activity); and/or c) inter-seizure interval (defined as the time (in seconds or minutes) elapsed between the onset of consecutive seizures) (see Osorio et al., Epilepsia 1998; 2002; EJN, 2009; PRE 2010).

(45) As indicated above, an impact that seizures may have on a patient may be quantified using various metrics described herein. For example, a partial seizure may result in a fall during which the patient fractures a leg bone. The occurrence of a fracture, even though this seizure's SSI and ISI values would not qualify it as extreme, may be used to declare the partial seizure as an extreme epileptic event. As another example, a complex partial seizure may result in a patient being dismissed from work causing a decrease in the patient's general quality of life (described below in further detail). This occurrence may prompt the device, process, or system of embodiments herein to indicate that an extreme epileptic event has occurred. Additionally, the frequency and/or ISI(s) of generalized and partial seizures may indicate an extreme epileptic event or state. The examples of generalized and partial seizure extreme epileptic events are exemplary in nature, and the described examples are not exclusive or limiting.

(46) Seizure metrics may include energy, defined for example as the product of peak intensity and duration, or as the product of the logarithm of the standard deviation of the difference of signals (e.g., EKG) and the duration. If Z(t) is the reference EKG signal then its difference from a test epoch will be X(t)=Z(t)−Z(t−1).

(47) These seizure metrics may be derived not only from cortical electrical activity, to date the only signal used for this purpose, but from kinetic (e.g., movement, acceleration or force of the body or body parts), cognitive (e.g., awareness, memory), cardiac (e.g., heart rate or heart rate variability), respiratory (e.g., rate, tidal volume, oxygen saturation), metabolic (e.g., pH), tissue stress markers

(e.g., lactic acid) or endocrine activity (e.g., cortisol) which provide valuable and reliable information about seizures such that they may be used in lieu of or in addition to electrical cortical activity. For example, the product of peak heart rate and the time it spends above values not observed during seizures may be used to estimate seizure severity.

(48) Severity may also be a seizure metric from which a seizure severity index (SSI) may be determined. The SSI may be observable/measurable data associated with a seizure that is quantifiable. Severity may be defined for example as the average of the sum of percentile intensity, duration and extent of spread of changes caused in the brain and other body organs, or as the sum of energies at each brain site engaged in seizure activity or at each organ affected by said seizure activity. In some embodiments, the SSI may be determined based upon one or more of the duration of the seizure event, the peak intensity of the seizure event and the spread of the seizure event. In some embodiments, the SSI may be determined based upon the duration of the seizure event and the peak intensity of the seizure event. In some such embodiments, the SSI may be calculated as the product of the peak intensity of the seizure event and the duration of the seizure event.

(49) The peak intensity may be the maximum value of any one, or any number, of body data values during a seizure event. For example, heart rate, an autonomic index, may be used to compute an SSI as follows: a) As an exemplary illustration, if a patient's mean inter-ictal (in-between seizures) heart rate is 80 beats/minute, the peak ictal heart rate is 150 beats/minute and the increase in heart rate above inter-ictal values lasts for 40 seconds, the SSI is either 6000 if the peak heart rate is used or 2800 if instead the net increase is taken into account. As a further exemplary illustration, the "area under the curve" may be also utilized to compute the SSI; b) If a patient's mean inter-ictal oxygen saturation during wakefulness is 98% and during a convulsion it drops to a minimum of 60%, remaining below the inter-ictal baseline for 60 seconds, the SSI based on this index, is 60×60=3600, or 33×60=1980 if instead the net decrease is used. In this example, an SSI above a pre-determined (or adjustable) value may indicate a risk of an extreme epileptic event/state (e.g., status epilepticus). Similarly, an SSI value above or below a pre-determined (or adjustable) percentile based upon historical patient data may indicate an increased risk of occurrence of an extreme event. For example, if an SSI value for a patient is above the ninetieth percentile of the patient's past SSI values, the patient may be at an increased risk for being in an extreme epileptic state (e.g., status epilepticus). The SSI computations described above are provided for exemplary purposes; other type of computations may also be implemented and remain within the spirit and scope of embodiments disclosed herein.

(50) In one embodiment, an SSI value indicative of the severity of a seizure may be determined based upon a body data as described above. In one embodiment, the determined SSI value may be compared to one or more of a reference value (e.g., inter-ictal or non-seizure value), a non-extreme seizure reference value or to or an extreme reference value that may or may not include a status epilepticus value. The status epilepticus value(s) may be based upon at least one of a past SSI value, a mean SSI value, a median SSI value, a mode SSI value, a percentile SSI value, a normalized SSI value, a distribution of SSI values, or to any other statistical transformation of an SE index or observable SE index change. Another useful measure for seizure time series is a post-ictal severity index (PISI) which may be defined as the intensity, duration and/or extent of spread (and changes therein) during the post-ictal state, compared to the inter-ictal or to the ictal state.

(51) Inter-seizure interval (ISI) may also be a seizure metric, and may be defined as the time (in any unit of time) elapsed between the onset of consecutive or non-consecutive seizures, or between the end of a seizure and the start of the next one. In one embodiment, inter-seizure intervals (ISIs) indicative of the time elapsed for example, between the end time and onset time of seizures, may be determined based at least upon body data and by performing statistical analyses to obtain measures of central tendency (e.g., mean) after appropriate statistical transformations if indicated, distributions either temporal, spatial or both, and the like. It should be noted that depending upon how the ISI is defined, seizure activity may be contained within this interval. Specifically, if the ISI

is defined as the time from the onset of a seizure to the onset of the next seizure, seizure activity is contained therein (see, e.g., inter-seizure intervals **1790**, **1796** and **1798** of FIG. **17**A below; each contain seizure activity). The determined ISI value(s) may be compared to non-extreme reference or to an extreme reference value(s). The ISI values may be obtained through direct recording of neuronal/neuropil activity from any potential or known epileptogenic brain site or indirectly through the recording of body signals (e.g., other neurologic, autonomic, metabolic, endocrine, tissue stress markers, etc.) that are under control of the potentially epileptogenic brain regions. In one embodiment, the duration of ISIs may be determined for each patient. Further, reference ISI values for a patient, groups or types of patients or types of seizures or of epilepsies, may be determined. These groups may include patients by gender, by age or range of ages, by level of physical fitness/body integrity, by the environment and conditions of said environment, by circadian or ultradian cycles, by level of consciousness, by type and level of cognitive or physical activity, by type of treatment(s) for seizures or other disorders etc. In one embodiment, a database for storing various categories of ISI values may be provided. This database may be used by the MD **200** to perform the assessment of extreme seizure events described herein.

(52) Classification of seizures as extreme events may be based on a) ISI duration said duration being for example, one standard deviation below the mean of ISI values or below the 10.sup.th percentile of ISI values; or b) the occurrence of seizure before at least one of a plurality of body signal indices has recovered to its inter-ictal value.

(53) Extreme ISIs may increase one or more of SSIs, seizure impact and/or seizure burden, because of the cumulative negative effect on one or more of the body signals used for their detection and quantification. For example, extreme ISIs may result in higher heart rates, more cognitive dysfunction, higher cortisol levels, more profound metabolic acidosis, and/or the like, as well as longer recovery (e.g., to baseline levels) than non-extreme ISIs.

(54) In one embodiment, ISI values may be based upon based upon at least one of a time between the onset of a first seizure and the onset of the next seizure, a time between the beginning of the post-ictal period of a first seizure and the onset of the next seizure, a time between the end of the post-ictal period of a first seizure and the onset of the next seizure, a time between the beginning of the post-ictal period of a first seizure and the beginning of the post-ictal period of the next seizure, or a time between the beginning of the post-ictal period of a first seizure and the end of the post-ictal period of the next seizure.

(55) A seizure may be considered extreme (independent of its SSI or ISI or spread values), if it causes system dysfunction of a type, magnitude, duration and/or frequency exceeding the ictal or post-ictal baseline dysfunction for that subject, or if the seizure adversely affects the subject's physical (including the neurologic system) integrity.

(56) The concept of "extreme" may take different meanings for different fields. Extreme value theory in math is a specific corpus in which limit theorems have been developed for the extreme of maximum value of a set of N variables. The term "extreme" as used herein may or may not have this mathematical connotation.

(57) Classifying a seizure event as "extreme" may be based upon a deleterious impact upon (or seriousness in relation to) the patient's health (e.g., falls, bone fractures, cardiac and/or respiratory dysfunction, memory loss, etc), and well being (e.g., depression) or the condition of the patient's disease state (e.g., worsening of epilepsy). In different cases, extreme seizure events may be classified according to other standards as well, and need not necessarily be specifically limited to those described herein. Similarly, extreme seizure events may be a combination of the above described classifications. An extreme seizure state may result in coma, cardio-respiratory failure, metabolic acidosis, liver and/or renal failure, bed sores, bone fractures, tissue hypoxia and brain damage. In one embodiment, an extreme epileptic state is defined as two or more extreme events occurring in close temporal proximity to each other.

(58) In one embodiment, determining whether an event is extreme may be based, at least in part,

upon: a) an ISI value being shorter than a reference ISI value; b) an occurrence of a first seizure followed by a second seizure, wherein the second seizure occurs prior at least one of either an autonomic, neurologic, endocrine, metabolic, tissue stress marker or physical fitness/body integrity returning to inter-ictal values, but being independent of the ISI value. In addition to examining the ISI value, SSI or other index values may also be used to determine whether an extreme event has occurred.

(59) Those skilled in the art having the benefit of this disclosure will appreciate that non-Gaussian distributions may be normalized by, for example, applying to the data logarithmic transformations so that mean, standard deviation and other measures may be more easily estimated. The approach of treating certain seizures as extreme events lends itself to a statistical or probabilistic approach for the prevention of status epilepticus through their anticipation or early detection.

(60) The following "metrics" expressed as indices, alone or in any combination, may be used to classify seizures into extreme as compared to non-extreme:

(61) 1. Magnitude and/or rate of increase in seizure energy or intensity, duration or extent of spread (referred to herein as the seizure severity index (SSI)). The SSI may be derived from one or more of these three metrics in any combination and using a useful mathematical approach. For example, the SSI may correspond to the area under the curve of the seizure plot); 2. Magnitude and/or rate and/or duration of increase/decrease and of extent of spread, of changes in body indices (e.g., heart activity, arterial pH and others) after the end of a seizure compared to inter-ictal or ictal values, referred herein to as a post-ictal severity index (PISI); 3. Magnitude and/or rate and/or extent of recovery from the post-ictal to the inter-ictal state of any body index; 4. Inter-seizure interval duration including the conditional probability of time to the next seizure given the time elapsed since the last seizure; 5. Seizure frequency per unit time, and/or cumulative seizure severity index (SSI) per unit time; 6. Cumulative post-ictal severity index per unit time compared to inter-ictal or ictal index values 7. Magnitude and/or duration and rate of change in level of consciousness as measured using available coma scales such the Glasgow scale or qualitative classification (e.g., deep coma, superficial coma, stupor, lethargy, awake but confused) as also used in clinical practice, compared to a baseline consciousness level; 8. Magnitude, duration (when applicable, e.g., when the patient is awake) and/or rate of changes in one or more cognitive functions as measured, for example, using a reaction time or any other validated neuropsychologic test; 9. Magnitude and/or duration and/or extent of spread in brain energy (electrical or metabolic, as measured using appropriate tools; 10. Magnitude, duration and/or rate of changes in autonomic indices such as heart rate, heart rate variability, heart rhythm, EKG, blood pressure, respirations, catecholamines, temperature and/or galvanic skin resistance, among others; 11. Magnitude, duration and/or rate of changes in metabolic indices such as arterial pH, SaO_2, CO_2, glucose and/or electrolytes, among others; 12. Magnitude, duration and/or rate of changes in endocrine indices such prolactin, cortisol, and/or growth hormone among others; and 13. Magnitude, duration and/or rate of change in tissue stress markers such as Reactive oxygen and nitrogen species including but not limited to iso- and neuro-prostanes and nitrite/nitrate ratio, gluthatione, gluthatione disulfide and gluthatione peroxidase activity, citrulline, protein carbonyls, thiobarbituric acid, the heat shock protein family, catecholamines, lactic acid, N-acetylaspartate, when applicable, free radicals, CK, Aldolase, troponin, and/or the like or of their metabolited when applicable. Comparisons of the above listed metrics and of all the indices listed below, may be made by taking into account time of day, level of consciousness of the patient (e.g., awake or asleep), level of physical activity (e.g., resting versus moving about) at the time the measurements were made, age, gender and physical fitness/health status or physical integrity.

(62) In one embodiment, body index may refer to one or more of an autonomic index, a neurologic index, a metabolic index, an endocrine index, a tissue stress index, a physical fitness/body integrity index, and/or a quality of life index. One or more of these body indices may be based upon body data, such as data relating to an autonomic signal, a neurologic signal, a metabolic signal, an

endocrine signal, a tissue stress signal, a physical fitness/body integrity signal, or a quality of life signal. The body index values may refer to values computed from one or more body signals detected by one or more sensors operatively coupled (e.g., implanted within, in contact with, or wireless coupled to the patient's body). Further, a morphology of the body signal indices may be used determine an amount of deviation of the body indices under from predetermined reference values. That is, the shape of the distribution of the body index may be analyzed and compared to reference values to identify one or more of a pathological or non-pathological patient state.

(63) In one or more embodiments, index values indicative of the function the autonomic, neurologic, endocrine, metabolic, gastro-intestinal, and/or of tissue/organ stress, such as those listed below, along with processes and tools for measuring and/or deriving these signals and markers, may be used to determine the occurrence of seizure events and to classify them as either non-extreme or extreme: I. Autonomic: a) Cardiac: Intra-cardiac pressure, cardiac volume, the ratio of intra-cardiac pressure to cardiac volume, ejection fraction, blood flow, cardiac wall temperature, heart rate variability (HRV), rate of change of HRV as a function of heart rate, heart sounds, heart rhythm, heartbeat wave morphology, point of maximum impulse force, thoracic wall deflection as measured with suitable tools such as EKG, phonocardiogram (PKG), Echocardiography, Apexcardiography (ApKG), and/or the like; b) Vascular: arterial and or venous pressure, arterial and/or venous blood wave pressure morphology, arterial and/or venous blood flow velocity, arterial and/or venous blood flow sounds, arterial and/or venous temperature as measured with suitable tools such as pressure, Doppler, sound, ultrasound and/or the like; c) Respiratory: tidal volume, minute volume, respiratory wave morphology, respiratory sounds, intercostal electromyography (EMG), diaphragmatic EMG, at least one chest wall and/or abdominal wall motion, respiratory rate (RR), rate of change of RR, arterial gases concentrations, oxygen saturation, end-tidal CO_2, as measured with suitable tools; d) Dermal: skin resistance, skin temperature, skin blood flow, sweat gland activity as measured with suitable tools; e) Neurotransmitters: concentrations of catecholamines and/or catecholamine metabolites, acetylcholine and/or acetylcholinesterase activity in body fluids or other tissues with suitable assays; rate of change of catecholamines, acetylcholine and/or acetylcholinesterase activity as measured from body fluids or other tissues with suitable assays, II. Neurologic a) Cognitive/Behavioral: level of consciousness, level of attention, reaction time, memory, visuo-spatial, language, reasoning, judgment, calculations, auditory and/or visual discrimination as measured using validated tests; b) Kinetic: force of muscle contraction, body movement direction, speed, acceleration, trajectory of movements in one, two and/or three dimensions, pattern and/or quality of movements, head, eyes, limb/body posture and/or position, body part orientation and/or position in reference to each other, body part orientation and/or position in reference to one or more predetermined axes or fiducials (e.g., body incline), muscle tone, agonist-to-antagonist muscle tone ratio, gait, accessory movements, falls as measured with suitable tools; c) Vocalizations: formed and/or unformed vocalizations as measured with suitable tools; d) Electroencephalography (EEG), Electrocorticography (ECoG), evoked potentials, field potentials, single unit activity as measured with suitable tools, III. Endocrine: a. prolactin, luteinizing hormone, follicle stimulation hormone, growth hormone, adreno-corticotropin hormone (ACTH), cortisol, vasopressin, beta-endorphin, beta, lipotropin, corticotropin-releasing factor (CRF) as measured from body fluids or other tissues with suitable assays; IV. Tissue Stress Markers: a. reactive oxygen and/or nitrogen species from the list comprising iso- and neuro-prostanes and nitrite-nitrate ratio, gluthatione, gluthatione disulfide and gluthatione peroxidase activity, citrulline, protein carbonyls, thiobarbituric acid, a heat shock protein family, catecholamines, lactic acid, N-acetylaspartate, metabolites of citrulline, protein carbonyls, thiobarbituric acid, a heat shock protein family, chromogranin A, free radicals or reactive oxygen species, catecholamines, lactic acid or N-acetylaspartate; as measured from body fluids or other tissues with suitable assays, V. Metabolic: a. arterial pH, arterial gases, lactate/pyruvate ratio, electrolytes and glucose as measured from body fluids or other tissues with suitable assays.

(64) The increased probability of subclinical and clinical pharmaco-resistant seizures to occur in clusters (see FIG. **15**), an observation previously made for clinical seizures only, and the decreased probability of seizure occurrence with increasing time from the last one (see e.g., FIG. **17**B) may be interpreted as: (i) reflecting the inherent capacity of seizures to trigger seizures; (ii) indicative of some form of seizure interdependency or plasticity ('memory') in the system, as recently proposed; and/or (iii) a clinically useful observation that in the embodiments herein may be exploited to anticipate and prevent extreme epileptic events including but not limited to status epilepticus.

(65) In one more embodiments, the method comprises either anticipating and preventing or identifying and/or managing an occurrence of an extreme epileptic event/state both with a certain probability, based upon a comparison of the determined SSI value to a reference or upon models based among other factors on the temporal evolution of SSI, patient seizure impact (PSimp) or ISI values or both. In one embodiment, the impact of the seizure is measured not only on each of the organ/systems of the body, but on the entire body as well.

(66) Although not so limited, methods and apparatus capable of implementing embodiments of the present invention are described below. In the context of this description, a medical device (MD) or medical system may also be referred to as an implantable medical device and/or an implantable medical device/system (IMD). It is contemplated that such a device and/or system may be implantable or non-implantable/non-implanted in various embodiments without departing from the spirit and scope of the invention. That is, when an implantable medical device/system (IMD) is described in one or more embodiments, it is also contemplated that a corresponding non-implanted or non-implantable may be used in one or more alternate embodiments and vice versa. In other embodiments, some portions of the system may be implanted while other portions may be external to the patient's body.

(67) Turning now to FIGS. **1**A-**1**C, stylized medical systems (MDs) **100** for implementing one or more embodiments of the present invention are depicted. These drawings and MDs **100** are described in A Systems Approach to Disease State and Health Assessment (FIGS. **3**A-**3**C) by Dr. Ivan Osorio (U.S. application Ser. No. 12/816,357), incorporated herein in its entirety. It is noted that the described MDs **100** may be implantable/implanted or non-implantable/non-implanted without departing from the spirit and scope of embodiments described herein.

(68) Turning now to FIG. **2**, a block diagram depiction of a medical device (MD) **200** is provided, in accordance with one illustrative embodiment of the present invention. In some embodiments, the MD **200** may be implantable (such as implantable electrical signal generator **110** from FIG. **1**), while in other embodiments the MD **200** may be completely external to the body of the patient.

(69) The MD **200** (such as generator **110** from FIG. **1**) may comprise a controller **210** capable of controlling various aspects of the operation of the MD **200**. The controller **210** may include a processor **215**, a memory **217**, etc., for processing and storing data respectively. The processor **215** may comprise one or more microcontrollers, microprocessors, etc., capable of performing various executions of software and/or firmware components. The memory **217** may comprise various memory portions where a number of types of data (e.g., internal data, external data instructions, software codes, status data, diagnostic data, etc.) may be stored. The memory **217** may comprise one or more of random access memory (RAM), dynamic random access memory (DRAM), electrically erasable programmable read-only memory (EEPROM), flash memory, etc. In one embodiment, a memory **217** may be separate from, but communicatively coupled to the controller **210**.

(70) The controller **210** is capable of receiving internal data or external data, and in one embodiment, is capable of processing body data to identify an extreme epileptic event in a patient. For example, the controller **210** may receive data from a body data collection module **275** (described further below) or from a memory **217**. Upon receiving the data or body data, the processor **215** may process the data in accordance with various embodiments described herein. For example, in one embodiment, the process may be adapted to compare values associated with two or

more body data indices. The processor **215** may also provide processed data/body data to other modules and units in the MD **200**. The controller **210** is capable of causing a therapy unit **220** to take responsive action in response to the identification of one or more various extreme or non-extreme epileptic events by the MD **200**, or by a patient, a physician, a nurse or caregiver, etc. In one embodiment, the responsive action may comprise generating and delivering an electrical signal to target tissues of the patient's body for treating a medical condition. In one or more embodiments, the responsive action may comprise drug treatments, oxygen treatments, cooling and/or the like. For example, the controller **210** may receive manual instructions from an operator externally, or may cause the electrical signal to be generated and delivered based on internal calculations and programming. In other embodiments, the MD **200** does not comprise a therapy unit **220**. In either embodiment the controller **210** is capable of affecting, and/or may be adapted to affect, substantially all functions of the MD **200**.

(71) As stated above, in one embodiment, the MD **200** may also comprise a therapy unit **220** capable of generating and delivering electrical signals to one or more electrodes **126**, **128** via leads **201** (FIGS. **2B**, **2D**) (and/or other therapies such as drugs, thermal energy, oxygen and/or the like). A lead assembly such as lead assembly **122** (FIG. **1**) may be coupled to the MD **200**. Therapy may be delivered through the leads **201** comprising the lead assembly **122** by the therapy unit **220** based upon instructions from the controller **210**. The therapy unit **220** may comprise various circuitries, such as electrical signal generators, impedance control circuitry to control the impedance "seen" by the leads, and other circuitry that receives instructions relating to the delivery of the electrical signal to tissue. Electrical signals delivered to a body part for therapeutic purposes may be of constant current (to compensate for impedance changes) or of constant voltage. The therapy unit **220** is capable of delivering electrical signals over the leads **201** comprising the lead assembly **122**. As should be apparent, in certain embodiments, the MD **200** does not comprise a therapy unit **220**, lead assembly **122**, or leads **201**. In particular, although FIGS. **2B** and **2D** are illustrated with therapy unit **220**, leads **201** and electrodes **126**, **128**, in alternative embodiments, these structures and the stimulation function enabled thereby may be omitted.

(72) In other embodiments, a lead **201** is operatively coupled to an electrode **126**, **128**, wherein the electrode **126**, **128** is adapted to couple to at least one of a portion of a brain structure of the patient **190**, a cranial nerve of a patient, a spinal cord of a patient **180**, a sympathetic nerve structure of the patient, a peripheral nerve of the patient, a dermis and/or subdermis of a patient.

(73) The MD **200** may also comprise a power supply **230**. The power supply **230** may comprise a battery, voltage regulators, capacitors, etc., to provide power for the operation of the MD **200**, including delivering the therapeutic electrical signal. The power supply **230** comprises a power source that in some embodiments may be rechargeable. In other embodiments, a non-rechargeable power source may be used. The power supply **230** provides power for the operation of the MD **200**, including electronic operations and the electrical signal generation and delivery functions. The power supply **230** may comprise a lithium/thionyl chloride cell or a lithium/carbon monofluoride (LiCFx) cell if the MD **200** is implantable, or may comprise conventional watch or 9V batteries for external (i.e., non-implantable) embodiments. Other battery types known in the art may also be used.

(74) The MD **200** may also comprise a communication unit **260** capable of facilitating communications between the MD **200** and various devices. In particular, the communication unit **260** is capable of providing transmission and reception of electronic signals to and from a monitoring unit **270**, such as a handheld computer or PDA that can communicate with the MD **200** wirelessly or by cable. The communication unit **260** may include hardware, software, firmware, or any combination thereof.

(75) The MD **200** may also comprise one or more sensor(s) **212** coupled via sensor lead(s) **211** to the MD **200**. The sensor(s) **212** are capable of receiving signals related to a body parameter, such as the patient's heart beat or a body chemical, and delivering the signals to the MD **200**. In one

embodiment, the sensor(s) **212** may be the same as implanted electrode(s) **126**, **128** (FIG. **1**). In other embodiments, the sensor(s) **212** are separate structures that may be placed on the patient's skin, such as over the patient's heart or elsewhere on the patient's body. It will be appreciated by persons of skill in the art that in some embodiments, lead **211** may be omitted and the MD **200** may communicate wirelessly with sensor **212**.

(76) The MD **200** may also comprise a body data collection module **275**. The body data collection module **275** may be adapted to, and/or capable of, collecting data relating to the body of a patient. Such data may be obtained using electrical, chemical, optical, biophotonic, acoustic (e.g., ultrasound), thermal sensors, pressure sensors, bioassays, chemical methods, imaging technology and/or motion sensors in any useful combination (these measurements may be performed at one or multiple spatial scales simultaneously or sequentially (e.g., multiplexing) and include but are not limited to: 1. Neurologic data such as neuronal electrical activity, neurotransmitter concentrations and their rate(s) of release and uptake, Kreb's and other cycle compounds, other chemical compounds (e.g., electrolytes, tissue stress markers), CSF and brain tissue pressure, temperature, and/or kinematic/kinetic activity, including but not limited to posture and fine motor movements among others using imaging techniques (e.g., video), accelerometers, inclinometers, actigraph devices, and/or the like; 1a. Level of consciousness and/or cognitive signals (e.g., attention, reaction time, memory, etc), neurological tests administered manually and/or automatically for qualitative or quantitative analyses; 2. Cardiac signals (e.g., as discussed above); 3. Body fluids signals including, but not limited to, those that may recorded using pressure, flow velocity and degree of laminarity (or turbulence) (e.g., Doppler), temperature, pH, chemical makeup (e.g., electrolytes, enzymes, tissue stress markers, anti-oxidants, gases); 4. Respiratory rate, pattern, tidal volume, and/or degree of activity of principal and/or accessory respiratory muscles to compute, for example, ratios (e.g., abdominal wall motion/thoracic wall motion, end tidal CO_2); 5. Endocrine indices (e.g., as discussed above); 6. Metabolic parameters (e.g., as discussed above); and 7. Kinetic data (e.g., as discussed above). This list is not exclusive, and the body data collection module **275** may collect additional data not listed herein, that would become apparent to one of skill in the art having the benefit of this disclosure. The body data collection module **275** may collect body data via one or more body data units (described in further detail below with respect to exemplary embodiments shown in FIGS. **3** & **4**, [**361-368**]). The body data units, as shown below, may be internal to the MD **200**, or external to, and communicatively coupled to, the MD **200**. All data comparisons may be made taken into consideration including, but not limited to, ultradian, circadian or infradian variations, gender, body mass index, age, past and present treatments (e.g., drugs, electrical signal therapy, and/or the like), physical fitness/integrity, etc.

(77) The body data collection module **275** may, in some embodiments, organize or process portions of the body data collected. Additionally, the body data collection module **275** may store or buffer the body data before sending the body data to other components of the MD **200**. In accordance with one embodiment, the body data collection module **275** may send some or all of the body data collected by the body data collection module **275** to the controller **210** for processing. In other embodiments, the body data collection module **275** may send collected body data to other components of the medical device instead of, or in addition to, the controller **210**; such other components include, but are not limited to, a SUDEP risk determination unit **285**, a seizure severity ranking unit **299**, a seizure severity index (SSI) unit **295** and an extreme epileptic event/state detection, quantification and risk determination unit **290**. The body data collection module **275** may also send the body data to the monitoring unit **270** or remote device(s) **292** via communication unit **260**.

(78) The MD **200** may also comprise a seizure spread, duration and intensity determination unit **294**. In accordance with one embodiment, the seizure spread, duration and intensity determination unit **294** may determine the amount of spread the seizure event and/or extreme seizure event. In other words, the greater the seizure spread, the more areas of the brain and/or body organs are

affected by the seizure event and/or extreme seizure event. The seizure spread, duration and intensity determination unit **294** may make such a determination based upon body data information, external indications, and/or other data that would become apparent to one of skill in the art having the benefit of this disclosure.

(79) The seizure spread, duration and intensity determination unit **294** may be adapted to provide seizure duration data which may include the duration of a patient's seizure event. The duration of a seizure event may be determined as the time that any of the autonomic, neurologic, metabolic, endocrine, or stress tissue marker indices values differ from inter-ictal and/or post-ictal values. In some embodiments, electrographic or clinical onset may be approximated by other body parameters, e.g., heart rate, kinetic activity, etc. In alternative embodiments, the duration of a seizure event may be determined as the time a body data value, a site(s) data value and/or an intensity, duration and spread data value (or value(s) respectively related thereto) is above or below adaptable and/or pre-determined threshold(s) and/or separatrix(tices). In further embodiments, the duration of a seizure event may be based on other criteria as would be apparent to one of skill in the art having the benefit of this disclosure. The seizure spread, duration and intensity determination unit **294** may also be adapted to determine a time spent in a seizure event state over a given time period or window (e.g., macroscopic as defined above); such a determination may include one or more seizure events occurring within the time period (as discussed in further detail below with respect to FIG. **13**). The time periods/windows may be of a fixed duration or may be of adjustable duration; likewise, the time period or window may move with or without overlap.

(80) The seizure spread, duration and intensity determination unit **294** may be adapted to provide seizure intensity data which may include the energy associated with a patient's seizure event. As described above, seizure intensity may be defined as the value of any one, or any number, of body data values during a seizure event. A maximum intensity of a seizure may be defined as the maximum value of any one, or any number, of body data values during a seizure event (e.g., the maximum heart rate of a patient during a seizure event).

(81) The MD **200** may also comprise a seizure severity index (SSI) unit **295**. SSIs may be calculated in some embodiments using at least two of seizure intensity, duration or extent of spread and using at least of one autonomic, endocrine, metabolic, stress tissue marker signals. For example, SSI may be the product of intensity and spread or the sum of intensity, duration and spread using one or more organ/system indices. In accordance with one embodiment, the SSI unit **295** may determine one or more seizure severity indices (SSIs) based upon the body data collected by the body data collection module **275** and/or other relevant data. An SSI may be a scalar-valued function of one or more body data variables that simplifies a possibly complex set of body information down to a single number: the SSI. In accordance with one embodiment, the SSI may be any statistic (or scalar-valued function) associated with a seizure with the property values that reflect some aspect of the severity of the corresponding seizures and may be ordered/sorted so that the distance between the SSI values for different seizures can be measured, compared and/or interpreted to provide meaningful information. In one embodiment, the SSI may be a quantity whose variation over a period of time measures the change in some body data or body phenomenon. In one embodiment, the SSI may be intended to generally reflect the impact of a seizure on a body organ or system. The SSI may also be a statistic associated with the seizure that enables comparison between different seizures, and the values for different seizures may be ordered/sorted and the distance (in a Euclidian or non-Euclidian sense) between them measured/compared/interpreted to provide meaningful information. If the SSI values describe the severity of the seizure not in absolute terms, but in a manner relative to other seizures for that patient (or relative to other patients), the SSI may be referred to as a "Relative SSI." Additionally, when more than one SSI is used at the same time, the plurality of SSIs may be combined into a single SSI by weighted averaging, and/or the like.

(82) The MD **200** may also comprise an inter-seizure interval index unit **245**. In accordance with

one embodiment, the inter-seizure interval index unit **245** may determine an index based upon inter-seizure interval. The inter-seizure interval index may, in some embodiments, be representative of the current inter-seizure interval relative to past single values, sets or values or value distributions and/or expected inter-seizure intervals, either for a specific patient or for one or more patients or patient populations. The inter-seizure interval index unit **245** may make such rankings based upon body data information, external indications (e.g., the patient's environment or surroundings), a patient's past seizure data, a normalized seizure data distribution, expected seizure data and/or other data that would become apparent to one of skill in the art having the benefit of this disclosure. Additionally, the inter-seizure interval index unit **245** may base its index upon a comparison of any or all of the above referenced data, information or indications.

(83) Inter seizure intervals (ISIs), post-ictal severity indices (PISIs), seizure severity indices (SSIs) and patient seizure impact (PSimp) may be used alone or in combination to determine the probability that an extreme event will occur, is occurring or has occurred. These data may be derived using one or more autonomic (e.g., cardiac, respiratory, dermal), endocrine (e.g., prolactin), metabolic (e.g., arterial pH), tissue stress markers (e.g., CK) or neurologic (e.g., kinetic, cognitive) signals.

(84) In one more embodiments identifying an occurrence of an extreme event with a certain probability or an increased risk of an extreme event state with a certain probability may be based upon a comparison of a determined SSI, ISI or PSimp values or upon models based, among others, on the temporal evolution of SSI, ISI or PSimp (for a specific patient or patient populations) in any combination.

(85) The MD **200** may also comprise a seizure (extreme seizure) ranking unit **247**. In accordance with one embodiment, the seizure (extreme seizure) ranking unit **247** may determine a ranking of a seizure event and/or extreme seizure based upon severity, ISI, PISI, PSimp, PSB and/or other factors. In one or more embodiments, the seizure (extreme seizure) ranking unit **247** may rank either seizure events or extreme seizure events. That is, in various embodiments, the seizure (extreme seizure) ranking unit **247** may be used for ranking one of seizure events or extreme seizure events. Alternatively, in one embodiment, multiple instances of the seizure (extreme seizure) ranking unit **247** may be implemented in the MD **200** (e.g., one instance for ranking seizure events and one instance for ranking extreme seizure events). As such, specific determinations relative to seizure events and/or extreme seizure events may be made independently of each other. For instance, a library or report log of just extreme seizure events may be maintained; this may allow for extreme seizure event comparisons and rankings which need not include non-extreme seizure events.

(86) The ranking of seizure events and/or extreme seizure events may, in some embodiments, be based upon a reference value that may in turn be based upon normative, reference and/or historical patient data, or the like, which may be patient-specific or for particular patient populations. In the case of extreme events, an extreme reference value may be used. An extreme reference value may be a reference value above and beyond that used to indicate non-extreme seizure events. In other words, the seizure (extreme seizure) ranking unit **247** may make such rankings based upon body data information, external indications, a patient's past seizure data and/or other data that would become apparent to one of skill in the art having the benefit of this disclosure. Additionally, the seizure (extreme seizure) ranking unit **247** may base its ranking(s) upon a comparison of any or all of the above referenced data, information or indications.

(87) The MD **200** may also comprise a site(s) of seizure origin determination unit **293**. In accordance with one embodiment, the site(s) of seizure origin determination unit **293** may determine the site or sites of origin of a seizure event and/or extreme seizure event in a patient's brain. This information may be used to determine different types of seizure events, rank them according to severity (SSI), ISI, PISI, PSimp and/or PSB according to site of origin and classify them as extreme or non-extreme events. The site(s) of seizure origin determination unit **293** may

make such a determination based upon body data information, external indications, and/or other data that would become apparent to one of skill in the art having the benefit of this disclosure. In one embodiment, patients in whom seizures originate from more than one brain site ("focus") within a region, one region in a lobe, one lobe within a hemisphere and/or one hemisphere, SSI, ISI, PISI, PSimp and/or PSB values may be determined from each site, region, lobe and/or hemisphere by performing statistical analyses to obtain measures of central tendency (e.g., mean), distributions (either temporal, spatial or both), and comparing the determined SSI value to reference/extreme reference value(s) that may or may not include a status epilepticus value. The status epilepticus value may be based upon at least one determination of if a status epilepticus event is occurring or the probability that it may occur.

(88) The MD **200** may also comprise a seizure determination module **299**. In accordance with one embodiment, the seizure determination module **299** may determine whether or not a patient has had, or is having, a seizure/extreme seizure event using body data. The seizure determination module may make such a determination based upon body data information, external indications, and/or other data that would become apparent to one of skill in the art having the benefit of this disclosure.

(89) The MD **200** may also comprise a patient seizure impact (PSimp) unit **296**. In accordance with one embodiment, the PSimp unit **296** may determine one or more seizure impact indices (PSimps) based upon the body data collected by the body data collection module **275** and/or other relevant data. The PSimp provides information not contained in the SSI (or in the inter-seizure interval index (ISI)) with regard to the effect of a seizure upon one or more body organs or parts. Two seizures (e.g., convulsions) with identical SSI may have a different impact on a patient: If during one such seizure (SSI=2200) the patient is walking downstairs, falls down suffers skull and rib fractures and brain contusions and during another seizure (SSI=2200) the patient is sitting down and drops onto a carpeted floor and does not suffer any injuries, the PSimp of the first seizure is considerable higher than that of the second one. Yet another example may be a patient whose overall health and body state is diminished by successive, similar seizure events and/or extreme seizure events after which the patient is not able to return to baseline with respect to one or more body parameters. Given the patient's diminished state, a subsequent, similar seizure event and/or extreme seizure event may have a more detrimental impact upon the patient than the previous, similar seizure events and/or extreme seizure events.

(90) The PSimp may be a function of a patient's health, age, physical fitness/integrity, circumstances, conditions and activities the patient is performing as a seizure occurs. That is, PSimp, depends on the time of day (day vs. night) patient's body state (e.g., body position), condition of one or more organ(s), level of physical activity (e.g., running vs. lying down), location of the patient (swimming in a pool vs. lying down in bed), state of alertness (awake vs. asleep), and the like.

(91) In accordance with one embodiment, the PSimp may be any statistic (or scalar-valued function) that reflect some aspect of the impact of seizures on a patient and may be sorted out and ranked so that the PSimp for different seizures can be measured, compared and/or interpreted to provide meaningful information. If the PSimp values describe the impact of the seizure not in absolute terms, but in a manner relative to other seizures for that patient (or relative to other patients), the PSimp may be referred to as a "Relative PSimp." Additionally, when more than one PSimp is used at the same time, the plurality of PIs may be combined into a single PSimp by weighted averaging, and/or the like. Furthermore, the PSimp alone (e.g., independent of SSI or ISI) may determine whether or not a seizure event is classified as extreme. In the example above, while the two seizures' SSIs are identical (**2200**), the one associated with bone fractures and brain contusion is extreme while the other is not. The PSimp value may be indicative of a risk of extreme events or states such as status epilepticus, SUDEP, body injuries and/or the like.

(92) In one embodiment, the PSimp unit **296** may be adapted to perform a method, comprising

receiving body data relating to at least one of an autonomic signal, a neurologic signal, an endocrine signal, a metabolic signal, or a body injury scale; identifying a seizure event based upon said body data; determining at least one PSimp value (quantitatively or qualitatively) reflective of the severity of said seizure event based at least upon said body data; comparing said determined at least one PSimp value to at least one reference value or extreme reference value; and identifying at least one of an occurrence of an extreme seizure event or an occurrence of a non-extreme seizure event, said identification being based upon at least the comparison of said determined PSimp value to said at least one reference value or extreme reference value. The SSI unit **295**, which may be incorporated into the PSimp unit **296** in one or more embodiments, may be adapted to and/or be capable of making a qualitative assessment of the PSimp value, such as: non-existent, mild, moderate and severe. The SSI unit **295** may be adapted to and/or be capable of determining a scaled value associated with said PSimp value based at least upon a quantitative assessment of the PSimp value; and assigning said PSimp value to a PSimp ranking unit.

(93) The PSimp also increases specificity of event detection and getting performance closer to the goal of "zero false positives." That is, if a seizure event and/or an extreme seizure event impacts a patient, the seizure event and/or an extreme seizure event would be unequivocally detected and/or identified. The impact of a seizure event and/or an extreme seizure event may be detected in any number of ways. In other words, even if a seizure event and/or an extreme seizure event is not detected based upon metrics based for example on heart rate and respirations directly indicative of an ictal state, its impact on the patient's health or quality of life (QOL) and mental health, would be detectable. This indirect impact may or may not be perceived by the patient or the caregivers but it may be determined, logged and recorded in one embodiment of this invention. For example, cumulative decline in heart rate variability as a function of recurring seizures, a change associated with an increased mortality risk that cannot be perceived by the patient or by caregivers without resorting to sophisticated statistical analyses, may be tracked, quantified, logged and recorded in one embodiment of this invention. Similarly, other unperceived extreme metrics may be quantified in addition to, or instead of, the logging of the impact and/or PSimp value.

(94) In one or more embodiments, the PSimp unit **296** may also comprise a patient seizure burden (PSB) unit **273** adapted to determine a seizure burden on the patient and in another embodiment the PSB unit **273** may be separate from the PSimp unit **296**. PSB is determined by measuring the magnitude of change (e.g., decline), rate of change of any and all of body organs/systems through analysis of any or all of their indices. PSB may be also determined by identifying the appearance of abnormalities in any body organs/systems, quantifying them and logging the results and time of occurrence of changes for future comparisons. For example, a highly relevant neurologic index, such as memory may be measured over time using validated tests and the scores may be used to determine if there is deterioration in this index, its magnitude and rate of change. In one embodiment, statistical analysis (e.g. regression analysis) may be performed to better identify the seizure contribution to the deterioration in certain or to the appearance of abnormalities (e.g. multi-focal PVCs). To this end, the indices used to measure PSB are for example correlated with the sum of SSI values over a time window (e.g., macroscopic) or a window based on some other time scale, or with the sum of SSI values per unit time multiplied by the time spent in seizure per unit time. Other means to determine the role of seizure in the patient's deterioration are: a) the sum of SSI values over a time window divided by mean or median inter-seizure interval (IR) value over that time window; b) the sum of SSI and post-ictal severity indices (PISI) over a time window or the sum of SSI and PISI multiplied by the sum of times spent in the seizure and post-ictal states over that time window; c) Seizure temporal density defined as the time spent in seizure over a time window divided by the number of seizure events over that time window; d) a product of time spent in seizure and the mean or median SSI value over that time window, divided by the number of seizures over that time window; e) the relation of an SSI or ISI value to other values/measures at different times. It should be noted that seizure burden may vary due to the time of day/night: one or

more extreme/non-extreme values may be chosen as a reference value for times of sleep or wakefulness. That is, when calculating and comparing a seizure burden, it may be useful to compare the seizure burden value to one obtained at same time of day or state (i.e., morning to morning, sleep-to-sleep and/or resting to resting).

(95) In addition to the PSimp and PSB measures, comparisons of SSI, PISI and/or ISI values to historical values allows quantification of the evolution of epilepsy as a function of time, therapies and preventive measures. For example, by plotting SSI values on the y-axis over a time window (x-axis) trends in the direction of improvement, worsening or stabilization of epilepsy may be easily determined. Increases in SSI or PISI values and/or decreases in ISI as a function of treatment may require a warning and appropriate therapy/treatment.

(96) In another embodiment, a quality of life (QOL) unit **274** may be incorporated into the PSimp unit **296** to determine the impact of epilepsy and seizures on a patient's QOL. The QOL unit **274** may be adapted to determine/quantify one or more QOL factors for a patient, such as mood, sense of well-being (or lack of it thereof), sexual activity and/or the like. The determination of various QOL factors may be used in the calculation/determination of PSB. In yet another embodiment, the physical fitness/integrity index unit **355** and the physical fitness/integrity determination unit **376** may be incorporated into PSimp unit **296** or in into a PSB unit **273** to determine the impact of the physical fitness/integrity index on the PSB. Decreases in fitness/integrity as documented using fitness/integrity measures may be correlated for example with SSI as detailed above to determine its contribution to loss of fitness/integrity).

(97) The MD **200** may also comprise an extreme epileptic event/state detection, quantification and risk determination unit **290**. In accordance with one embodiment, the extreme epileptic event/state detection, quantification and risk determination unit **290** may determine a current state and/or a future risk of entering a status epilepticus state. In one embodiment, the extreme epileptic event/state detection, quantification and risk determination unit **290** may identify a status epilepticus event from a group consisting of a present status epilepticus state, a past status epilepticus state or an increased risk of a status epilepticus state. The determination and/or identification of a risk/state of an extreme event such as status epilepticus may be made based in part or whole upon a comparison of one or more SSI, PISI and/or ISI values to a status epilepticus threshold value(s) or to a reference/extreme reference value that may in turn be based upon reference, normative and/or historical patient data, or the like.

(98) The MD **200** may also comprise an extreme epileptic event confirmation unit **287**. In accordance with one embodiment, the extreme epileptic event confirmation unit **287** may confirm that a patient is having an extreme epileptic event and that said event is status epilepticus. The extreme epileptic event quantification and confirmation unit **287** may also confirm that a patient remains in a state of status epilepticus subsequent to an initial detection/identification of the state of status epilepticus.

(99) The MD **200** may also comprise a state assessment unit **288**. In accordance with one embodiment, the state assessment unit **288** may indicate various states of a patient's disease, including but not limited to, a status epilepticus event, a risk of SUDEP, a current seizure event, variations in body data indicative of an event/change of a patient's disease state, and the like. In one embodiment, the indication may be provided to other components within the MD **200**, to the monitoring unit **270** and/or database unit **250** and/or local database unit **255**, to a remote device **292**, to the PSimp unit **296**, to the PSB unit **273**, to a patient, to a caregiver or physician, or the like. The state assessment unit **288** may further indicate that the state or change in state of the patient's disease should be logged, for example, in database unit **250**, local database unit **255**, and/or the like.

(100) The MD **200** may also comprise a warning unit **289**. In accordance with one embodiment, the warning unit **289** may issue a warning to a patient, physician and/or care giver. Such a warning may be indicative of various states of a patient's disease, including but not limited to, an extreme

epileptic event such as status epilepticus, a risk of SUDEP, a current seizure event, variations in body data indicative of an event/change of a patient's disease state, and the like, as described above with respect to the state assessment unit **288**. Additionally, the warning unit **289** may warn that an event presents an increased risk to the health and/or safety of the patient. The warning unit **289** may provide a warning for a patient, physician and/or care giver to take some immediate or otherwise urgent action related to the event/change of a patient's disease state. The warning unit **289** may warn in addition, or alternatively, to the indication provided by the state assessment unit **288** described above.

(101) The MD **200** may also comprise an event/warning button **235**. In accordance with one embodiment, the event/warning button **235** may be located external to the MD **200** in an implanted/non-implanted embodiment, or may be part of the MD **200** in non-implanted embodiments. The event/warning button **235** may be communicatively coupled to the MD **200** and/or to the monitoring unit **270** in various embodiments. The event/warning button **235** may allow for a patient or other individual (such as a caregiver, family member or emergency response personnel) to activate a warning to identify a seizure event and/or an extreme seizure event/state. Such activation may be used to warn of, treat and/or log a seizure event and/or an extreme seizure event/state. Additionally, in one or more embodiments, the event/warning button **235** may be used to elevate a warning or therapy for an existing seizure event and/or an extreme seizure event/state.

(102) In addition to components of the MD **200** described above, a non-implantable/implantable medical system may comprise a storage unit to store an indication of at least one of epilepsy event (e.g., a seizure or an increased risk of a seizure). The storage unit may be the memory **217** of the MD **200**, another storage unit of the MD **200**, or an external database, such as the local database unit **255** or a remote database unit **250**. The MD **200** may communicate the indication via the communications unit **260**. Alternatively or in addition to an external database, the MD **200** may be adapted to communicate the indication to at least one of a patient, a caregiver, or a healthcare provider.

(103) In various embodiments, one or more of the units or modules described above may be located in a monitoring unit **270** or a remote device **292**. For example, in one exemplary embodiment, the extreme epileptic event/state detection, quantification and risk determination unit **290** may be external to the MD **200**, e.g., in a monitoring unit **270** or a remote device **292**. Locating the extreme epileptic event/state detection, quantification and risk determination unit **290** outside the MD **200** may be advantageous if the status epilepticus risk determination or detection parameter calculation is computationally intensive, in order to reduce energy expenditure and heat generation in the MD **200** or to expedite calculation of the at least one status epilepticus risk determination or detection parameter.

(104) The monitoring unit **270** may be a device that is capable of transmitting and receiving data to and from the MD **200**. In one embodiment, the monitoring unit **270** is a computer system capable of executing a data-acquisition program. The monitoring unit **270** may be controlled by a healthcare provider, such as a physician, remotely at a base station, for example, from a doctor's office or also directly. In alternative embodiments, the monitoring unit **270** may be controlled by a patient in a system providing less interactive communication with the MD **200** than another monitoring unit **270** controlled by a healthcare provider. Whether controlled by the patient or by a healthcare provider, the monitoring unit **270** may be a computer, preferably a handheld computer or PDA, but may alternatively comprise any other device that is capable of electronic communications and programming, e.g., hand-held computer system, a PC computer system, a laptop computer system, a server, a personal digital assistant (PDA), an Apple-based computer system, a cellular telephone, etc. The monitoring unit **270** may download various parameters and program software into the MD **200** for programming the operation of the medical device, and may also receive and upload various status conditions and other data from the MD **200**. Communications between the monitoring unit **270** and the communication unit **260** in the MD **200** may occur via a wireless or

other type of communication, represented generally by line **277** in FIG. **2**. This may occur using, e.g., a wand **155** to communicate by RF energy with an MD **200**. Alternatively, the wand may be omitted in some systems, e.g., systems in which the MD **200** is non-implantable, or implantable systems in which monitoring unit **270** and MD **200** operate in the MICS bandwidths.

(105) Likewise, in various embodiments the remote device **292** may communicate with the monitoring unit **270**, and thus with the MD **200**, with communications between the remote device **292** and the monitoring unit **270** represented generally by line **297** in FIG. **2**. Communications between the monitoring unit **270** and the remote device **292** may occur via a wireless or other type of communication represented by line **277**.

(106) In one embodiment, the monitoring unit **270** may comprise a local database unit **255**. Optionally or alternatively, the monitoring unit **270** may also be coupled to a database unit **250**, which may be separate from monitoring unit **270** (e.g., a centralized database wirelessly linked to a handheld monitoring unit **270**). The database unit **250** and/or the local database unit **255** are capable of storing various patient data. This data may comprise patient parameter data acquired from a patient's body and/or therapy parameter data. The database unit **250** and/or the local database unit **255** may comprise data for a plurality of patients, and may be organized and stored in a variety of manners, such as in date format, severity of disease format, etc. The database unit **250** and/or the local database unit **255** may be relational databases in one embodiment. A physician may perform various patient management functions (e.g., programming parameters for a responsive therapy and/or setting thresholds for one or more event detection parameters) using the monitoring unit **270**, which may include obtaining and/or analyzing data from the MD **200** and/or data from the database unit **250** and/or the local database unit **255**. The database unit **250** and/or the local database unit **255** may store various patient data.

(107) The MD **200** may also comprise a logging/reporting module **265**. The logging/reporting module **265** may be adapted to log and/or store data related to the patient, the patient's physical condition, the patient's disease and disease state and/or any other body data. The logging/reporting module **265** may be adapted to log and/or store information indicative of events relating to the patient's disease (e.g., seizure events, data related to time of recovery after seizure events and/or patient sleep-wake cycles). The logging/reporting module **265** may also be adapted to log and/or store a timestamp indicative of the time and day on which stored data is/was acquired. The logging/reporting module **265** may be adapted to report stored data, or any portion thereof, to a patient, a physician, a care giver, an external computer **150**, a database unit **250**, a local database unit **255** and/or a remote device **292**. It is contemplated that the logging/reporting module **265** may not be present in the MD **200** in various embodiments, or alternatively, that the logging/reporting module **265** may be located in a monitoring unit **270** or a remote device **292**.

(108) One or more of the blocks illustrated in the block diagram of the MD **200** in FIG. **2**, may comprise hardware units, software units, firmware units, or any combination thereof. Additionally, one or more blocks illustrated in FIG. **2** may be combined with other blocks, which may represent circuit hardware units, software algorithms, etc. Additionally, any number of the circuitry or software units from the various blocks illustrated in FIG. **2** may be combined into a programmable device, such as a field programmable gate array, an ASIC device, etc.

(109) The medical device system, in one exemplary embodiment, provides for software module(s) that are capable of acquiring, storing, and processing various forms of data, such as patient data/parameters (e.g., body data such as heart rate, breathing rate, brain-activity parameters, PSimp data, PSB data (e.g., disease progression or regression data, quality of life data, etc.), and/or the like) as well as therapy parameter data (e.g., adverse effects). Therapy parameters may include, but are not limited to, electrical signal parameters that define therapeutic electrical signals delivered by the medical device in response to the detection of an epilepsy event, medication parameters and/or any other therapeutic treatment parameter. Therapy parameters for a therapeutic electrical signal may also include, but are not limited to, a current amplitude, a pulse width, a pulse shape, a

frequency, an on-time, an off-time, etc.

(110) In one exemplary embodiment, at least one electrode may be coupled of to each of two or more cranial nerves. (In this context, two or more cranial nerves mean two or more nerves having different names or numerical designations, and do not refer to the left and right versions of a particular nerve. However, bilateral (left and right) stimulation of the same nerve may be also carried out). In one embodiment, at least one electrode may be coupled to either or both vagus nerves or a branch of either or both vagus nerves. The term "operatively" coupled may include direct or indirect coupling. Each of the nerves in this embodiment or others involving two or more cranial nerves may be stimulated according to particular activation modalities that may be independent between the two nerves. In another embodiment, a therapy may be delivered directly to the brain.

(111) Turning now to FIG. **3**, a block diagram depiction of an MD **200** is provided, in accordance with one illustrative embodiment of the present invention. FIG. **3** depicts an exemplary implementation of the body data collection module **275** described above with respect to FIG. **2**. The body data collection module **275** may include hardware (e.g., amplifiers, accelerometers), tools for chemical assays, optical measuring tools, a body data memory **350** for storing and/or buffering data in the body data collection module **275**. The body data memory **350** may, in some embodiments, be adapted to store body data for logging or reporting purposes and/or for future body data processing and/or statistical analyses. The body data collection module **275** may also include one or more body data interfaces **310**. The body data interface **310** may provide an interface for input/output (I/O) communications between the body data collection module **275** and body data units/modules (e.g., [**360-370**], [**373-376**]) via connection **380**. Connection **380** may be a wired or wireless connection, or a combination of the two. The connection **380** may be a bus-like implementation or may include an individual connection (not shown) for each, or some number, of the body data units (e.g., [**360-370**], [**373-376**]). The connection **380** may also include connection elements as would be known to one of skill in the art having the benefit of this disclosure. In various embodiments, the body data units may include, but are not limited to, an autonomic data acquisition unit **360**, a neurologic data acquisition unit **370**, and endocrine data acquisition unit **373**, a metabolic data acquisition unit **374**, a tissue stress marker data acquisition unit **375**, a QOL unit **274** and/or a physical fitness/integrity acquisition and determination unit **376**. In one embodiment, the autonomic data acquisition unit **360** may include a heart beat data acquisition unit **361** adapted to acquire a phonocardiogram (PKG), EKG, echocardiophraphy, apexcardiography and/or the like, a blood pressure acquisition unit **363**, a respiration acquisition unit **364**, a blood gases acquisition unit **365**, and/or the like. In one embodiment, the neurologic data acquisition unit **370** may contain a kinetic unit **366** that may comprise an accelerometer unit **367**, an inclinometer unit **368**, and/or the like; the neurologic data acquisition unit **370** may also contain a responsiveness/awareness unit **369** that may be used to determine a patient's responsiveness to testing/stimuli and/or a patient's awareness of their surroundings. These lists are not exclusive, and the body data collection module **275** may collect additional data not listed herein, that would become apparent to one of skill in the art having the benefit of this disclosure. The body data units ([**360-370**], [**373-376**]) may be adapted to collect, acquire, receive/transmit heart beat data, EKG, PKG, echocardiogram, apexcardiogram, blood pressure, respirations, blood gases, body acceleration data, body inclination data, EEG/ECoG and/or the like.

(112) The body data interface(s) **310** may include various amplifier(s) **320**, one or more A/D converters **330** and/or one or more buffers **340** or other memory (not shown). In one embodiment, the amplifier(s) **320** may be adapted to boost and condition incoming and/or outgoing signal strengths for signals such as those to/from any of the body data units/modules (e.g., ([**360-370**], [**373-376**])) or signals to/from other units/modules of the MD **200**. The A/D converter(s) **330** may be adapted to convert analog input signals from the body data unit(s)/module(s) into a digital signal format for processing by controller **210** (and/or processor **215**). A converted signal may also be

stored in a buffer(s) **340**, a body data memory **350**, or some other memory internal to the MD **200** (e.g., memory **217**, FIG. **2**) or external to the MD **200** (e.g., monitoring unit **270**, local database unit **255**, database unit **250**, and remote device **292**). The buffer(s) **340** may be adapted to buffer and/or store signals received by the body data collection module **275** as well as signals to be transmitted by the body data collection module **275**. In various embodiments, the buffer(s) **340** may also be adapted to buffer and/or store signals in the body data collection module **275** as these signals are transmitted between components of the body data collection module **275**.

(113) As an illustrative example, in one embodiment, data related to a patient's respiration may be acquired by respiration unit **364** and sent to the MD **200**. The body data collection module **275** in the MD **200** may receive the respiration data using body data interface(s) **310**. As the data is received by the body data interface(s) **310**, the incoming data may be amplified/conditioned by amplifier(s) **320** and then converted by A/D converter(s) into a digital form. The digital signal may be buffered by a buffer(s) **340** before the data signal is transmitted to other components of the body data collection module **275** (e.g., body data memory **350**) or other components of the MD **200** (e.g., controller **210**, processor **215**, memory **217**, communication unit **260**, seizure determination module **299**, SSI unit **295**, extreme epileptic event/state detection, quantification and risk determination unit **290**, or the like). Body data in analog form may be also used in one or more embodiments.

(114) Turning now to FIG. **4**, an MD **200** (as described above in FIG. **3**) is provided, in accordance with one illustrative embodiment of the present invention. FIG. **4** depicts the body data units (FIGS. **3** & **4**, [**360-370**], [**373-376**]), in accordance with one embodiment, being externally coupled to the MD **200**, instead of being included within the MD **200** as shown in FIG. **3**. In accordance with various embodiments, any number and type of body data units (FIGS. **3** & **4**, [**360-370**], [**373-376**]) may be included within the MD **200**, as shown in FIG. **4** while other body data units (FIGS. **3** & **4**, [**360-370**], [**373-376**]) may be externally coupled, as shown in FIG. **3**. The body data units (FIGS. **3** & **4**, [**360-370**], [**373-376**]) may be coupled to the body data collection module **275** in a fashion similar to that described above with respect to FIG. **3** (**380**), or in any number of different manners used in coupling intra-medical device modules and units. It should be noted that the manner by which the body data units (FIGS. **3** & **4**, [**360-370**], [**373-376**]) may be coupled to the body data collection module **275** is not essential to and does not limit the embodiments described herein as would be understood by one of skill in the art having the benefit of this disclosure.

(115) Turning now to FIG. **5A**, a block diagram depiction of a seizure severity index unit **295** (SSI unit) is provided, in accordance with one illustrative embodiment of the present invention. In one embodiment, the SSI unit **295** may be adapted to determine a seizure severity index (SSI). The SSI unit **295** may use body data and/or seizure data (e.g., seizure intensity data, seizure duration data and/or seizure spread data) in determining the SSI. In one embodiment, body data collection module **275** may send body data to SSI unit **295**. In one embodiment, the SSI unit **295** may include at least one of a neurologic index unit **510**, an autonomic index unit **520**, an endocrine index unit **540**, a metabolic index unit **542** and/or a stress marker index unit **550** and/or a physical fitness/integrity index unit **555**. The neurologic index unit **510** may be adapted to determine a neurologic index value using neurologic body data from the body data collection module **275**. The autonomic index unit **520** may be adapted to determine an autonomic index value using autonomic body data from the body data collection module **275**. Examples of autonomic index may include, but are not limited to, heart rate variability heart rate, cardiac cycle morphology, respiratory rate, tidal volume, respiratory cycle morphology, oxygen saturation, and end tidal CO_2 saturation, etc. Examples of a cardiac cycle morphology may include, but are not limited to, a PQRST morphology, an ST interval, a QT interval, etc. Examples of a respiratory cycle morphology may include Cheyne-Stokes, ataxic breathing, apneustic breathing, etc.

(116) The endocrine index unit **540** may be adapted to determine an endocrine index value using

body data from the body data collection module **275**. The metabolic index unit **542** may be adapted to determine a metabolic index value using body data from the body data collection module **275**. The stress marker index unit **550** may be adapted to determine a stress marker index value using body data from the body data collection module **275**. The physical fitness/integrity index unit **555** may be adapted to determine a stress marker index value using body data from the body data collection module **275**. It is noted that the seizure determination module **299** may send seizure data to the SSI unit **295** and that units **510**, **520**, **540**, **542**, **550** and **555** may be adapted to determine their respective indices based on seizure data from seizure determination module **299**.

(117) The neurologic index unit **510**, autonomic index unit **520**, endocrine index unit **540**, metabolic index unit **542**, stress marker index unit **550**, and physical fitness/integrity unit **555** may be adapted to transmit their respective index values to an SSI value determination unit **530**. The SSI value determination unit **530** may use a neurologic index value, an autonomic index value, an endocrine index value, a metabolic index value, a stress marker index value, a physical fitness/integrity index determined by the seizure data, and/or other body data to determine a seizure severity index value (SSI value), as described above with respect to FIG. **2**. The SSI value may be transmitted/provided to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the warning unit **289**, the seizure (extreme seizure) ranking unit **247**, a memory **217**, a database **250/255**, a remote device **292**, and/or other components of the MD **200**. It is noted that in some embodiments the SSI value may be sent directly to the warning unit **289** and/or the seizure (extreme seizure) ranking unit **247** without being sent to the extreme epileptic event/state detection, quantification and risk determination unit **290**.

(118) Turning now to FIG. **5B**, a block diagram depiction of a patient impact unit **296** is provided, in accordance with one illustrative embodiment of the present invention. In one embodiment, the PSimp unit **296** may be adapted to include a seizure severity index (SSI) unit **295** or to use the data from a separate SSI unit **295**. The PSimp unit **296** or the PSB unit **273** may receive data from the physical fitness/integrity index unit **555**. In one embodiment, body data collection module **275** may send body data to PSimp unit **296**. Such body data may include, but is not limited to, neurologic and/or autonomic body data, endocrine data, stress marker data, physical activity data, and/or the like. Likewise, the seizure determination module **299** may send corresponding data to the PSimp unit **296**. The PSimp unit **296** may, in one embodiment, comprise a QOL index unit **544**. The QOL index unit **544** may provide a QOL index value for use in a PSimp determination, in accordance with one embodiment, or in other embodiments, the QOL index may be computed separately from the PSimp value. The PSimp value determination unit **531** may use seizure burden data, QOL data and/or other body data to determine a patient seizure impact value (PSimp value). The PSimp value may be transmitted/provided to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the warning unit **289**, a memory (**217**), a database **250/255**, a remote device **292**, and/or other components of the MD **200**.

(119) Turning now to FIG. **5C**, a block diagram depiction of an inter-seizure interval index unit **245** (ISI index unit) is provided, in accordance with one illustrative embodiment of the present invention. In one embodiment, the ISI index value determination unit **532** may use a neurologic index value, an autonomic index value, an endocrine index value, a stress marker index value, seizure data and/or other body data to determine an inter-seizure interval index value (ISI index value), as described above with respect to FIG. **2**. In one embodiment, the ISI index value may be indicative of extreme seizure events/states if the time interval between two or more seizures is below (by one or more standard deviations) the mean of a normalized distribution of ISIs or at or below the 20.sup.th percentile of distribution values. The ISI index value may be transmitted/provided to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the warning unit **289**, the inter-seizure interval ranking unit **1025**, a memory (**217**), a database **250/255**, a remote device **292**, and/or other components of the MD **200**. It is noted that in some embodiments the ISI value may be sent directly to the warning unit **289**

and/or the seizure (extreme seizure) ranking unit **247** without being sent to the extreme epileptic event/state detection, quantification and risk determination unit **290**.

(120) In one embodiment, the ISI index unit **245** may be adapted to determine an inter-seizure interval (ISI). The ISI index unit **245** may use the time of onset and/or termination of at least two consecutive or non-consecutive seizures from a seizure spread, duration and intensity determination unit **294** to calculate the time elapsed between the seizures. In one embodiment, the ISI index unit **245** may receive data from duration determination unit **1030** (see FIG. **11** below) and inter-seizure interval data from an inter-seizure interval determination unit **1020** (see FIG. **11** below), body data from the body data collection module **275** and/or other seizure data (not shown) in determining the ISI index. In one embodiment, body data collection module **275** may send body data to the ISI index unit **245**. Such body data may include, but is not limited to, neurologic and/or autonomic body data, endocrine data, stress marker data, physical activity data, and/or the like. Likewise, the seizure determination module **299** may send seizure data to the ISI index unit **245**.

(121) Turning now to FIG. **6**, a block diagram depiction of a warning unit **289** is provided, in accordance with one illustrative embodiment of the present invention. In one embodiment, the warning unit **289** may be adapted to provide a warning of a seizure, seizure events and/or extreme seizure events. In various embodiments, extreme seizure events may include a present or past state of status epilepticus, an increased risk of status epilepticus, a risk of SUDEP associated with a seizure, an increased risk of SUDEP associated with a seizure, the occurrence of injury or of an increased risk of injury and/or the like. The warning unit **289** may provide a warning to a patient, a physician, a caregiver, the logging/reporting module **265**, the monitoring unit **270**, the remote device **292**, the memory **217**, the database **250**/**255**, and/or the like.

(122) The warning unit **289** may include a warning generating unit **610**, in accordance with one embodiment. The warning unit **289** may be adapted to receive SSI data from the SSI Unit **295**, ISI data from the ISI Index Unit **245**, PISI data from the (post-ictal determination unit **1033**), physical fitness/physical integrity data from the physical fitness/integrity index unit **555**, PSimp data from the PSimp unit **296**, extreme epileptic event/state data from extreme epileptic event/state detection, quantification and risk determination unit **290**, and/or extreme seizure event confirmation data from extreme epileptic event confirmation unit **287**. In various embodiments, the warning unit **289** may be adapted to receive other signals and/or data in addition to, or alternatively to, the aforementioned data, as shown in FIG. **6**. In one embodiment, the warning generating unit **610** may take any data received by the warning unit **289** as an input to generate a warning. The warning may be a general warning related to a seizure or extreme seizure event or state such as status epilepticus, an upgrade in warning of an existing extreme seizure state/event, or related to an injury associated with a seizure (e.g., which prolongs the time the patient is immobile or in the recumbent position beyond a mean, median or percentile time for that patient). In one embodiment, the warning unit **289** may include an extreme epileptic event confirmation unit **287**. The extreme epileptic event confirmation unit **287** may take data from the extreme epileptic event/state detection, quantification and risk determination unit **290** and confirm or verify that an extreme epileptic event/state is likely, is about to occur, is occurring or has occurred. If the extreme event/state is confirmed by the extreme epileptic event/state determination unit **287**, the confirmation may be sent to the warning generating unit **610**, and the warning may proceed. If the extreme event/state is not confirmed by the extreme epileptic event/state determination unit **287**, the warning may be blocked or disabled, and data associated with the blocked/disabled warning may be removed from the logging/reporting module **265**, the monitoring unit **270**, the remote device **292**, the memory **217**, the database **250**/**255**, and/or the like.

(123) Warnings may include sounds or lights, automated emails, text messages, telephone calls, or video messages sent from the MD **200**, either directly or via a monitoring unit **270**, to the police, an EMT unit, the patient's physician/caregiver's cellular telephone, PDA, computer **150**, television, etc. Such warning(s) may allow the patient and/or caregivers to take measures protective of the

patient's well-being and those of others, e.g., pulling out of traffic and turning off a car, when the patient is driving; stopping the use of machinery, contacting another adult if the patient is providing childcare, removing the patient from a swimming pool or bathtub, lying down or sitting if the patient is standing, etc. The warning may, when appropriate, automatically disable operation of a vehicle or of power equipment or inflate a life saver (e.g., for a patient who is swimming) or bags placed on the chest or back of a patient to minimize risk of injury in case of falls.

(124) Turning now to FIG. **7**, a flowchart depiction of a method for taking action (e.g., warning, providing treatment/therapy, logging, etc.) in response to the occurrence of a seizure event and/or an extreme seizure event is provided, in accordance with one illustrative embodiment of the present invention. The MD acquires and/or receives body data at step **710**, typically from the body data collection unit **275** which buffers, amplifies/conditions and performs A/D conversion of the body data. Using data from unit **275**, the seizure determination module **299** in the MD **200** determines, through operations including but not limited to calculations based on at least one index, if a seizure event has occurred, is likely to occur or is occurring (step **720**). If the MD **200** determines that no seizure or seizure event has occurred, the MD **200** will continue to monitor for body data (step **730**; return the flow to step **710**).

(125) If the medical device determines (at step **720**) that a seizure event has occurred or is occurring or is likely to occur, based on at least one of an autonomic index, a neurologic index, a stress marker index, a metabolic index and/or an endocrine index (e.g., using an SSI unit **295**, an ISI index unit **245**, a PSimp unit **296** and/or another unit/module in the MD **200**), the subsequent step **740** may be to determine, e.g., using unit **290**, if the event is extreme. Determination that the event is extreme, may trigger responsive actions (step **750**) including but not limited to delivering a therapy or therapies, (unit **220**), warning(s) (unit **289**) and requesting confirmation via unit **287** that the event is extreme (step **755**), and if it is deemed extreme, it may be then ranked (step **760**), typically using unit **247**. If the event is not confirmed as extreme, all responsive actions may be terminated (step **770**). At any given step, information yielded by that step, and the decisions made based on this information, may be send to logging/reporting unit **265** (step **745**) and/or to memory **217**. Steps **750**, **760** and **770** may begin at the same time and end at the same time (or at different times) according to various embodiments. Further, it is contemplated that events may be logged after a determination and/or confirmation of an extreme event (steps **740**/**755**) has occurred.

(126) The number of steps and the order in which they are adopted may vary according to one of several possible embodiment contemplated herein. For example, confirmation that the event is extreme may be unnecessary if all indices (autonomic, neurologic, endocrine, metabolic, tissue stress marker, physical integrity, etc.) are determined simultaneously. However, if all indices are not measured, those untested may be determined in any number and/or temporal sequence for the purpose of confirmation. The medical device **200** may determine an SSI value using at least one of an autonomic index, a neurologic index, a stress marker index, a metabolic index and/or an endocrine index; the medical device **200** may determine an inter-seizure interval index (ISI index) value using at least one of an autonomic index, a neurologic index, a stress marker index, a metabolic index and/or an endocrine index; the medical device **200** may determine a physical fitness/integrity index value using at least one of an autonomic index, a neurologic index, a stress marker index, a metabolic index and/or an endocrine index. Typically, the SSI value is determined by SSI unit **295** (which may comprise an SSI determination unit (**530**)). Typically, the ISI index value is determined by ISI index unit **245**. Typically, the physical fitness/integrity index value is determined by physical fitness/integrity index unit **355**. In one or more embodiments, additional data may also be used to determine the ISI index value and/or physical fitness/integrity index value. Depending upon the embodiment, one or more of the SSI value, the ISI index value and/or the physical fitness/integrity index value may be determined. For example, in one embodiment, only the SSI value may be calculated while the ISI index value is not calculated. In another embodiment, only the ISI index value may be calculated while the SSI value is not calculated. In one or more

embodiments, additional data may also be used to determine the SSI values, ISI values and/or physical fitness/integrity index values.

(127) The confirmation of an extreme epileptic event/state parameter(s) may be performed by an extreme epileptic event/state confirmation unit **287** (at step **755**). The confirmation of an extreme epileptic event/state may be based upon one or more SSI values and/or one or more ISI index values as described above, and/or be based upon other data/indices as described above. From step **755**, the flow may proceed to determining a patient seizure impact (PSimp) value (step **780**), and in some embodiments, the flow may then proceed to determining a seizure burden value (step **790**). The medical device **200** may determine a PSimp value using at least one of an autonomic index, a neurologic index, a stress marker index, a metabolic index and/or an endocrine index, a quality of life index or a physical fitness/integrity index and or the like (step **780**). The medical device **200** may determine a seizure burden value using at least one of an autonomic index, a neurologic index, a stress marker index, a metabolic index and/or an endocrine index and/or the like (step **790**). Other procedures/modules may be used to determine a seizure burden and/or patient seizure impact. For example, an Acquire/Determine Physical Fitness Index/Body Integrity Unit (not shown) may use these data to determine seizure burden and/or patient seizure impact. The MD **200** may also take responsive action for extreme epileptic event/state (at step **750**) that may include, but is not limited to, drug/chemical therapy, electric stimulation, cooling, supportive care, oxygen administration, warning, logging/reporting, and/or the like. It is also contemplated that a patient's physical activity may be stored in a memory **217** or logged/reported in one or more of the database **250**/**255** and the remote device **292**.

(128) Turning now to FIG. **8**, details of the steps in FIG. **7** that are implemented when an extreme event is likely to occur, about to occur, is occurring or has occurred are provided, is depicted in accordance with one or more illustrative embodiments. The MD **200** may issue a warning or take action (step **890**) based upon detection of an extreme epileptic event/state in a patient (steps **810**/**820**). It should be noted that in some embodiments an extreme epileptic event is the occurrence of an actual extreme epileptic seizure or condition, while in other embodiments the extreme epileptic event is an elevated risk of an extreme epileptic seizure or condition. If the MD **200** determines a patient is not in an extreme epileptic event/state (step **820**), the MD **200** may proceed to record the current condition of the patient and reassess calculation(s) of extreme epileptic event/state data (**830**). If the MD **200** determines a patient is in an extreme epileptic event/state (step **820**), the MD **200** may in some embodiments perform an extreme epileptic event confirmation (step **860**). If the MD **200** determines a patient is in an extreme epileptic event/state (step **820**), the MD **200** may, in one embodiment, issue a warning and/or deliver treatment to the patient (step **890**).

(129) In one embodiment, the MD **200** may delay warning the patient until the extreme seizure event confirmation is confirmed (step **860**). It is contemplated that steps **860** and **890** may occur at the same time or at different times in various embodiments described herein. If the MD **200** determines an extreme seizure event confirmation has not occurred (**870**), the MD **200** records and/or logs a tentative and/or potential false positive event, e.g., by recording the original detection as erroneous or unconfirmed (step **880**), if this determination has not been based on all indices disclosed in this invention. In the case that all disclosed indices have not been used for said determination, one or more indices not used in issuing a "false positive" decision may be measured and depending on the results of the more comprehensive analysis, the decision ("false positive") may be confirmed or rejected. If a false positive event is issued, the medical device **200** may also disable (at least transiently) an issued warning and/or stop treatment and/or remove an event from the log (step **880**). If a false positive event is confirmed, this outcome may be recorded and/or logged in a logging/reporting module **265** (step **880**). If the false positive event is rejected, an extreme event detection may be re-issued and all responsive actions will be re-instituted according to the embodiments of this invention (e.g., steps **870**, **890**).

(130) Turning now to FIG. **9**, a flowchart depiction of a method for warning and/or providing a treatment to a patient in response to an extreme seizure event is provided, in accordance with one illustrative embodiment. The MD **200** may provide a warning of a state of an extreme epileptic event/state via the warning unit **289** in one or more embodiments (step **910**). The warning may be to a patient, a physician, a caregiver, emergency response personnel, a logging/reporting module **265**, a monitoring unit **270**, a remote device **292**, an external entity **265** and/or the like. The warning may indicate an extreme epileptic event/state (e.g., a severe seizure, status epilepticus, or an injury resulting from an otherwise non-extreme seizure). At step **912**, the decision is made whether or not to treat the patient based upon the warning from step **910**. If it is determined that no treatment will be performed, the flow proceeds to step **914** where patient monitoring and body data acquisition continues. If it is determined that treatment will be administered, the flow may proceed to one or both of steps **920** and/or **962**.

(131) A determination may be made as to which treatment modality(ies) are to be provided to a patient (step **920**). Modalities include, but are not limited to, electrical currents, chemical/drug therapies and/or supportive treatments such as cooling, fluids, pressor agents and/or oxygen. In one embodiment, the MD **200** may automatically implement a predetermined treatment to reduce the risk of an extreme epileptic event/state and/or to reduce the effects of a state of an extreme epileptic event/state in the patient (step **970**) using one or more treatment modalities. In reference to supportive care, seizures are powerful biological stressors and inductors of stress markers and may deplete the body of certain anti-oxidants such as glutathione peroxidase. The concentration of certain compounds that protect from biological stress (e.g., dehydroepiandrosterone or its sulfate conjugate, glutathione peroxidase and/or the like) or the body's total antioxidant capacity may be measured to determine if it is adequate, and if not, to increase it using available antioxidants to preserve the integrity of organs/functions so as to stall disease progression. Stress marker index indices and antioxidants may be measured in brain (invasively and/or non-invasively), CSF, plasma, serum, erythrocytes, urine, and saliva (e.g., alpha amylase).

(132) Upon delivery of automatic treatment(s), an assessment of the efficacy of the treatment may be performed (step **975**) in some embodiments. Based upon the assessment of the efficacy of treatment, a determination is made whether the state of the extreme epileptic event/state is at least substantially controlled (step **980**). If a determination is made that the extreme epileptic event/state is not substantially controlled (step **980**), the MD **200** may upgrade the warning to a more severe level (step **990**) and the treatment being delivered may be modified, and/or an additional treatment may be provided (step **995**). In an alternative embodiment, the step of upgrading the warning may be initially omitted and the treatment may be modified first, as indicated by the dotted line connecting blocks **980** and **995** and **990***a*. The MD **200** may then continue to determine whether the state of the status epilepticus is substantially controlled (step **980**).

(133) Upon a determination that the extreme event/state is substantially controlled (step **980**), the warning may be downgraded and/or canceled (step **985**). Further, the treatment parameter(s) used for the administration of the automatic treatment may be reported/logged (step **985**). The MD **200** may then continue to perform body data acquisition (step **914**).

(134) In one embodiment, upon providing a warning to the patient, caregiver, and/or to a healthcare provider (step **910**), the MD **200** may provide for the healthcare provider, the caregiver, and/or the patient to assume care/treatment responsibilities (step **962**). Based upon one or more inputs received by the MD **200**, a determination may be made as to whether to override the automated treatment (step **964**). If it is determined that the automated treatment is not to be overridden, then the state of the automatic treatment is maintained (step **966**).

(135) If a determination is made that the automated treatment is to be overridden, a non-automated treatment plan is determined and executed (step **967**). A more detailed description of the determining and executing a non-automated treatment plan is provided in FIG. **10** and accompanying description below. In one embodiment, upon determining and executing a non-

automated treatment plan, this treatment plan may be set as the next automatic treatment that is executed by the MD **200** (step **968**). The MD **200** then continues to perform body data acquisition (step **914**). In an alternative embodiment, the step of setting the non-automatic treatment plan as the default automatic treatment plan may be omitted, as indicated by the dotted lines between blocks **967**, **968** and **969**.

(136) Turning now to FIG. **10**, a stylized depiction of the step of determining an automatic or a non-automatic treatment plan of steps **967/970** of FIG. **9**, in accordance with one illustrative embodiment, is provided. The MD **200** may select a chemical/drug the dosage and rate of delivery (step **950**) and deliver the drug/chemical to the patient (step **960**). In addition to, or alternatively to, the chemical treatment, the MD **200** may select parameters of an electrical signal to treat the patient (step **930**) and apply the specified electrical signal to a neural structure (e.g., a branch of the vagus nerve) of the patient (step **940**). Further, in addition, or alternatively, the MD **200** may select one or more thermal parameters to specifically treat the extreme event/state with a thermal therapy (heating and/or cooling) (step **942**) and apply it (step **943**). In alternative embodiments, additional and/or other treatment modalities may be implemented, such as endosomatic therapies (e.g., biofeedback, sensory, and/or cognitive stimulation). The flow may then proceed to steps **968/969** and/or step **975**. Further, in addition, or alternatively, the MD **200** may select one or more supportive care steps to treat the patient (step **945**) and apply the specified supportive care (step **947**).

(137) Turning now to FIG. **11**, a block diagram depiction of a seizure (or extreme seizure) ranking unit **247** is provided, in accordance with one illustrative embodiment. Rankings reduce in-depth measures to a sequence of ordinal numbers, thus facilitating the evaluation of complex information according to certain criteria. Rankings, in embodiments described herein, may be done according to one or more of a so-called standard completion, modified, ordinal, dense or fractional ranking. Those skilled in the art having the benefit of this disclosure would appreciate the approach to ranking described herein, is applicable to the ranking of any measure or index in this invention.

(138) In one embodiment, the seizure (extreme seizure) ranking unit **247** may rank events classified as extreme using data from the extreme epileptic event/state detection, quantification and risk determination unit **290** and may provide the rankings to the memory (**217**), database **250/255**, and/or remote device **292**. In various embodiments, the seizure (extreme seizure) ranking unit, may receive data directly from, for example, the SSI unit **295**, ISI unit **245**, PSimp unit **296**, the seizure spread duration and intensity determination unit **293**, and/or the like, about seizure intensity data, seizure intensity rankings, inter-seizure interval data, inter-seizure interval ranking data, seizure duration data, time spent in seizure data, and/or the like. Seizure ranking unit **247** may also receive data from memory (**217**), database **250/255**, and/or remote device **292**. In one or more embodiments, the output of the seizure (extreme seizure) ranking unit **247** may be an indication of a seizure ranking as compared to historical seizure rankings and/or one or more reference values. This may be accomplished by first determining if an SSI and/or an ISI value are near, at, or outside the boundaries between extreme and non-extreme values. If an event fulfills the criteria to be classified as extreme, it is ranked relative to other extreme events, and the warning, treatment, etc., are upgraded based on said ranking (e.g., said event ranks above the 60.sup.th percentile for SSI and below the 40.sup.th percentile for ISI). For a normalized distribution the upgrade may take place if the extreme event is for example, one SD to the right of the mean or median for SSI and one SD to the left of the mean or median for ISI. It is contemplated that other percentile ranking values may be used.

(139) The seizure (extreme seizure) ranking unit **247** may include a seizure intensity ranking unit **1010**, in accordance with one or more embodiments. The seizure intensity ranking unit **1010** may be adapted to receive body data from body data collection module **275**, site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/intensity/duration data from seizure spread, duration and intensity determination unit **294**, SSI data from the SSI unit **295** and/or other data

from various components of the MD **200** and/or the seizure (extreme seizure) ranking unit **247**. It should be noted that these determinations of intensity recited herein are not exclusive, and the determination of seizure intensity data using other body data is also contemplated, as would be evident to one of skill in the art having the benefit of this disclosure. Seizure intensity data may be determined from site(s) of seizure origin data and/or at each site (brain and/or body) to where the seizure spreads or is manifested, whether directly or indirectly. In one embodiment, the seizure intensity ranking unit **1010** may determine seizure intensity data based upon data measurements over a period of time or body data as a function of time (as discussed in further detail below with respect to FIGS. **14-15**). In other embodiments, the seizure intensity ranking unit **1010** may determine seizure intensity data based only on one of intensity, duration or extent of spread. That is, intensity, duration and extent of spread may be ranked separately from SSI by the seizure (extreme seizure) ranking unit **247**. This approach allows classification of any of these three metrics as extreme, even if a composite measure incorporating all three (e.g., SSI=(percentile intensity+percentile duration+percentile spread)/3) may not be extreme. This may allow for better anticipation and for prevention of extreme epileptic events by allowing seizures to be classified as extreme based on one of the three metrics alone, even though the SSI may not be extreme based on two or more of them. Similarly, it may be advantageous to issue a certain kind of warning (different than the warning for an extreme SSI) and deliver a therapy in this instance. As such, it may be noted that there are: 1) extreme intensity and/or duration and/or spread; and/or 2) extreme events/states when the SSI is extreme. In various embodiments, seizure intensity data may be logged/reported in logging/reporting module **265**, transmitted to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, the memory **217**, the remote device **292** and/or the database **250**/**255**, as described above in FIG. **2**.

(140) The seizure (extreme seizure) ranking unit **247** may include a seizure duration ranking unit **1032**, in accordance with one or more embodiments. The seizure duration ranking unit **1032** may be adapted to receive body data from body data collection module **275** site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/intensity/duration data from seizure spread, duration and intensity determination unit **294** and/or other data from various components of the MD **200**. The seizure duration ranking unit **1032** may be adapted to determine seizure ranking data which may include the ranking of a patient's seizure event with respect to a reference value and/or compared with past seizure/extreme seizure events/states. In further embodiments, the rank of the duration of a seizure event may be based on other criteria as would be apparent to one of skill in the art having the benefit of this disclosure. The seizure duration ranking unit **1032** may also be adapted to determine a seizure duration ranking over a given time period; such a determination may include comparing one or more seizure events occurring within the time period (discussed in further detail below with respect to FIG. **13**). The time periods may be of a fixed duration or may be of dynamic duration; likewise, the time period may be a fixed window or a rolling window.

(141) The seizure (extreme seizure) ranking unit **247** may include a seizure spread ranking unit **1015**, in accordance with one or more embodiments. The seizure spread ranking unit **1015** may be adapted to receive body data from body data collection module **275** site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/intensity/duration data from seizure spread, duration and intensity determination unit **294** (described above) and/or other data from various components of the MD **200**. The seizure spread ranking unit **1015** may be adapted to determine a seizure spread ranking, i.e., a relative determination of a seizure spread relationship to past values. In one embodiment, for example, the seizure spread ranking may be based upon a normal/normalized distribution of seizure spread values. The spread of seizure events may be determined based upon body data, site(s) data and/or spread data values relative to adjustable or pre-determined thresholds, responsiveness and/or awareness of a patient, and/or the like. In various embodiments, seizure spread rankings may be logged/reported in logging/reporting module **265** and/or transmitted to the extreme epileptic event/state detection, quantification and risk

determination unit **290**, the SSI unit **295**, memory **217** and/or database **250/255**, as described above with respect to FIG. **2**.

(142) The seizure (extreme seizure) ranking unit **247** may include an inter-seizure interval ranking unit **1025**, in accordance with one or more embodiments. The inter-seizure interval ranking unit **1025** may be adapted to receive ISI data from the ISI determination unit **1020** (described below), body data from body data collection module **275**, site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/intensity/duration data from seizure spread, duration and intensity determination unit **294** and/or other data from various components of the MD **200**. The inter-seizure interval ranking unit **1025** may be adapted to determine an inter-seizure interval ranking, i.e., a relative determination of a seizure interval relationship to past interval values. In one embodiment, for example, the inter-seizure interval ranking may be based upon a normal/normalized distribution of seizure interval values. The beginnings and ends of seizure events may be determined based upon body data, site(s) data and/or spread data values relative to dynamic or pre-determined thresholds, responsiveness of a patient, and/or the like. In various embodiments, inter-seizure interval rankings may be logged/reported in logging/reporting module **265** and/or transmitted to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, memory **217** and/or database **250/255**, as described above with respect to FIG. **2**.

(143) The seizure (extreme seizure) ranking unit **247** may include an inter-seizure interval ISI) determination unit **1020**, in accordance with one or more embodiments. The inter-seizure interval determination unit **1020** may be adapted to receive body data from body data collection module **275**, site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/duration/intensity data from seizure spread, duration and intensity determination unit **294**, ISI data from the ISI index unit **245** and/or other data from various components of the MD **200**. The inter-seizure interval determination unit **1020** may be adapted to determine an inter-seizure interval (ISI), i.e., a time period between seizure events. In one embodiment, the inter-seizure interval may be measured from the end of one seizure event to the beginning of the next seizure event. In another embodiment, the inter-seizure interval may be measured from the onset of a first seizure to the onset of a second seizure. The beginnings and ends of seizure events may be determined based upon body data, site(s) data and/or spread data values relative to adjustable or pre-determined thresholds, responsiveness/awareness of a patient, and/or the like. In one embodiment, the time spent by a patient in a seizure event state (or the time spent in a seizure) may be quantified as one or more of a seizure duration plus ISIs or portions thereof. In various embodiments, inter-seizure interval data may be logged/reported in logging/reporting module **265** and/or transmitted to the ISI ranking unit **1025**, the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, memory **217** and/or database **250**/**255** as shown above with respect to FIG. **2**. In one or more embodiments, an epileptic event may be classified as extreme based upon on the ISI, or based upon the ISI in addition to other values described herein.

(144) In various embodiments, seizure duration data, seizure ranking data and/or the time spent in seizure data may be logged/reported in logging/reporting module **265** and/or transmitted to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, memory **217** and/or database **250/255** as described above with respect to FIG. **2**.

(145) The seizure (extreme seizure) ranking unit **247** may include a post-ictal ranking unit **1034**, in accordance with one or more embodiments. The post-ictal ranking unit **1034** may be adapted to receive post-ictal data from post-ictal determination unit **1033**, body data from body data collection module **275** site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/duration/intensity data from seizure spread, duration and intensity determination unit **294** and/or other data from various components of the MD **200**. The post-ictal ranking unit **1034** may be adapted to determine post-ictal ranking data which may include the ranking of a patient's post-

ictal state with respect to a reference value and/or compared with past post-ictal states. In further embodiments, the rank of the post-ictal state of a seizure event may be based on other criteria as would be apparent to one of skill in the art having the benefit of this disclosure. The post-ictal ranking unit **1034** may also be adapted to determine a post-ictal ranking over a given time period; such a determination may include comparing one or more seizure events occurring within the time period (discussed in further detail below with respect to FIG. **13**). The time periods may be of a fixed or a dynamic duration; likewise, the time period may be a fixed window or a rolling window.

(146) The seizure (extreme seizure) ranking unit **247** may include a post-ictal determination unit **1033**. In one embodiment, the post-ictal state may be defined as the state in which the values of any of the indices disclosed herein are different from those observed in the inter-ictal and ictal states. The post-ictal determination unit **1033** may be adapted to receive body data from body data collection module **275** site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/duration/intensity data from seizure spread, duration and intensity determination unit **294** and/or other data from various components of the MD **200**. In accordance with one embodiment, the post-ictal determination unit **1033** may determine the duration of a post-ictal state of a patient. The post-ictal index determination **1033** may also determine a severity of the post-ictal state based upon the magnitude and/or duration and or spread of the post-ictal state, as well as the rate of change into and out of a post-ictal state, in manners similar to those used in the described embodiments herein for determining SSI. In one embodiment, the magnitude of the post-ictal state may be measured as the area below a lower threshold and above the curve graphically representing a seizure parameter (see, e.g., FIGS. **14**B/**17**B and accompanying descriptions). The post-ictal index determination **1033** may make such determinations based upon body data information, external indications, and/or other data that would become apparent to one of skill in the art having the benefit of this disclosure. A prolonged and/or an increased duration and/or magnitude of the post-ictal state may be indicative of a severity of a seizure event experienced by a patient and used to classify an event as extreme or non-extreme. Moreover, continued increases in post-ictal state duration and/or magnitude may be indicative of a patient's having a risk/increased risk of an extreme seizure event and/or a patient having an extreme seizure event, such as, but not limited to status epilepticus. Additionally, shortened inter-ictal periods compared to a reference inter-ictal value(s) may provide an additional and/or independent indication of a patient's having a risk/increased risk of an extreme seizure event and/or a patient having an extreme seizure event, such as, but not limited to status epilepticus. In various embodiments, post-ictal data may be logged/reported in logging/reporting module **265** and/or transmitted to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, memory **217** and/or database **250**/**255** as shown above with respect to FIG. **2**. It is noted that those of ordinary skill in the art having the benefit of this disclosure will appreciate that the duration of inter-ictal states may be given by the times the body is not in the ictal or post-ictal states.

(147) The seizure (extreme seizure) ranking unit **247** may include a seizure impact (PSimp) ranking unit **1017**, in accordance with one or more embodiments. The seizure impact ranking unit **1017** may be adapted to receive PSimp data from PSimp unit **296**, body data from body data collection module **275** site(s) data from the site(s) of seizure origin determination unit **293**, seizure spread/intensity/duration data from seizure spread, duration and intensity determination unit **294**, physical fitness/integrity data acquisition and determination unit **376**, and/or other applicable and/or other data from various components of the MD **200** or from external sources such as physician's/caregiver's reports and/or tests results. The seizure impact ranking unit **1017** may be adapted to determine a seizure impact ranking, i.e., a relative determination of a seizure impact relationship to past values. In one embodiment, for example, the seizure impact ranking may be based upon a normal/normalized distribution of seizure impact values. The impact of seizure events may be determined based upon body data, site(s) data and/or spread data values relative to adaptable or pre-determined thresholds, responsiveness of a patient, and/or the like. Those of skill

in the art would appreciate that quantitative or qualitative scales may be developed for each patient of for a population of patients. In various embodiments, seizure impact rankings may be logged/reported in logging/reporting module **265** and/or transmitted to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, memory **217** and/or database **250**/**255**, as described above with respect to FIG. **2**.

(148) The seizure (extreme seizure) ranking unit **247** may include a QOL ranking unit **1012**, in accordance with one or more embodiments. QOL ranking unit **1012**, may receive data from QOL determination unit **274** (described above), from PSimp determination unit **296** or from PSimp ranking unit **1017** as well as from other units such seizure intensity ranking unit **1010** whenever applicable or useful. Additionally the QOL ranking unit **1012** may receive data from QOL questionnaires/instruments, structured or unstructured interviews of the patient as well as impressions, opinions or comments from the patient or caregivers. In various embodiments, QOL rankings may be logged/reported in logging/reporting module **265** and/or transmitted to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, memory **217** and/or database **250**/**255**, as described above with respect to FIG. **2**.

(149) The seizure (extreme seizure) ranking unit **247** may include a seizure burden ranking unit **1018**, in accordance with one or more embodiments. In one embodiment, the seizure burden ranking unit **1018** may be adapted to receive seizure burden data from seizure burden unit **273**, body data from body data collection module **275** site(s), from the PSimp unit **296**, from the PSimp ranking unit **1017** and/or from the QOL ranking unit **1012** and/or from external sources such as a physician's/care-giver's report(s) or test(s) results. In another embodiment seizure burden ranking unit **1018** may receive data from the site(s) of seizure origin determination unit **293**, seizure spread/intensity/duration data from seizure spread, duration and intensity determination unit **294** and/or other data from various components of the MD **200** or from external sources such as a physician's/caregiver report and/or tests results. The seizure burden ranking unit **1018** may be adapted to determine a seizure burden ranking, i.e., a relative determination of a seizure burden relationship to historical interval values, normative values and/or expected values. In one embodiment, for example, the seizure burden ranking may be based upon a normal/normalized distribution of seizure burden values. The burden of seizure events may be determined based upon body data, site(s) data and/or spread data values relative to adaptable or pre-determined thresholds, responsiveness of a patient, and/or the like, using time windows of at least one length. In various embodiments, seizure burden rankings may be logged/reported in logging/reporting module **265** and/or transmitted to the extreme epileptic event/state detection, quantification and risk determination unit **290**, the SSI unit **295**, memory **217** and/or database **250**/**255**, as described above with respect to FIG. **2**.

(150) In one or more embodiments, the seizure duration ranking unit **1032**, seizure spread ranking unit **1015**, the seizure intensity ranking unit **1010**, the seizure spread, duration and intensity determination unit **294**, inter-seizure interval ranking unit **1025**, the inter-seizure interval determination unit **1020**, QOL ranking unit **1012**, QOL unit **274**, post-ictal ranking unit **1034**, post-ictal determination unit **1033**, PSimp ranking unit **1017**, PSimp unit **296**, seizure burden ranking unit **1018**, seizure burden unit **273** and/or site(s) of seizure origin determination unit **293** may transmit information to and from each other for the purposes of determining their respective data outputs.

(151) Seizure duration, intensity, extent of spread, ISI and all of their mathematical transformations, seizure burden and PSimp may be analyzed and interpreted in the context of for ultradian, circadian, or infradian rhythms (if present) and if trends are observed, said trends may be used to improve estimation of risks of having an extreme event. The efficacy of therapies may be also assessed in the context of these rhythms and optimized as needed, using these observations.

(152) Turning now to FIG. **12**, a flowchart depiction of a method for taking action (warning, treating and/or logging) in response to determining a seizure event (extreme seizure event/state) is

provided, in accordance with one illustrative embodiment of the present invention. The medical device **200** acquires and/or receives body data at (step **1210**). Typically, the body data collection unit **275** receives the body data. The body data may be indicative of whether or not a seizure or extreme seizure event has occurred or is occurring. After performing buffering, amplification/conditioning and A/D conversion of the body data, the medical device **200** determines if a seizure is about to occur, is occurring or has occurred (step **1220**). Typically the seizure determination module **299** makes this determination based upon one or more calculations. If the medical device **200** determines that no seizure or seizure event has occurred, the medical device **200** will continue to monitor for body data (step **1230** and return the flow to step **1210**).

(153) If the medical device determines (at step **1220**) that a seizure is about to occur, is occurring or has occurred, the method proceeds to acquire seizure intensity data (step **1240**), seizure duration data (step **1245**), extent of seizure spread data (step **1247**), time spent in seizure data (step **1250**) and/or inter-seizure interval data (step **1250**). In one embodiment, indices are acquired and/or determined using an SSI unit **295** (typically comprising an autonomic index unit **520**, a neurologic index unit **510**, an endocrine index **540**, a metabolic index **542** and/or a tissue stress marker index unit **550**). Steps **1240**, **1245**, **1247**, **1250** and/or **1255** may begin at the same time and end at the same time (or at different times and in different combinations) according to different embodiments contemplated herein. In other words, steps **1240**, **1245**, **1247**, **1250** and/or **1255** may begin and be completed substantially in parallel (i.e., at approximately the same time or at the same time) or independently of each other. The medical device determines an SSI value, an ISI index value and/or a seizure burden value using the seizure intensity data, seizure duration data, time spent in seizure data and/or inter-seizure interval data (step **1260**). Typically, the SSI value is determined by SSI unit **295** (which may comprise an SSI determination unit (**530**), as described above with regard to FIG. **11**). In one or more embodiments, additional data may also be used to determine the SSI value.

(154) Still referring to FIG. **12**, once an SSI value is determined (step **1260**), the flow may proceed to step **1270**. The medical device **200** calculates one or more parameters related to an extreme epileptic state/event (step **1270**). The calculation of extreme epileptic state/event parameter(s) may be performed by an extreme epileptic event/state detection, quantification and risk determination unit **290**. The calculation of extreme epileptic state/event parameter(s) may include a calculation using one or more SSI values. Upon calculating extreme epileptic state/event parameter(s), the MD **200** may log the parameters into memory, e.g., in a database (step **1272**). The extreme epileptic state/event parameter(s) may be stored in an external memory (e.g., the database unit **250** and/or the local database unit **255**), and/or in memory that is internal to the MD **200** (e.g., memory **217**). The status epilepticus parameters may also be sent to an external device **265**. From step **1270**, the flow may proceed to the processing of extreme epileptic state/event data (step **1275**). The medical device **200** may also take responsive action (at step **1275**) such as a warning performed by warning unit **289** which may comprise a warning generation unit **610**. In one or more embodiments, the responsive action may be taken according to (or similar to) the flowchart depicted in FIGS. **7-9** and **12**.

(155) Turning now to FIG. **13**, a seizure energy probability density function (PDF) is depicted, according to one embodiment. For patients with pharmaco-resistant seizures, who are most in need of this invention, the probability of a seizure having energy larger than x is proportional to x.sup. −β, where β≈−⅔, wherein β refers to the exponent of the PDF (the exponent of the probability density function is (1+β)). Accordingly, seizure energy may be inversely correlated with the probability of its occurrence. Therefore, in instances where seizure energy is higher, probability of seizure occurrence may be lower. The slight deviation from linearity indicated in FIG. **13** may be due to the presence of characteristic scales in the probability density function of seizure energy of some patients. The curves of FIG. **13** exemplify one of the statistical approaches for determining if an epileptic seizure event corresponds to status epilepticus. Seizures with energies above

5×10.sup.4 (x-axis) are very severe (but infrequent) and could correspond to extreme events. Seizure energy (estimated, for example, as the product of peak seizure intensity and duration) may be used interchangeably with seizure severity.

(156) Turning now to FIG. **14**A, one example of a probability density function of inter-seizure intervals (ISI) is illustrated. According to one embodiment, an estimate relating to a probability density function for inter-seizure intervals may be defined as the time elapsed from the onset of one seizure to the onset of the next. FIG. **14**A illustrates that very short inter-seizure intervals could also indicate an increased risk of extreme events.

(157) In one embodiment, a predictive analysis may be derived from the heavy tail structure of the inter-seizure interval distributions between successive events. The predictive analysis may indicate that the longer the elapsed time period since the occurrence of the previous seizure event, the longer the expected time until the next seizure event. (See, e.g., Osorio et al., PRE 2010).

(158) Turning now to FIG. **14**B, a graphical depiction of the temporal boundaries/metrics of: three states of interest: a) inter-ictal (defined as the period of time during which the value of an index is different from ictal and post-ictal values); b) ictal (defined as the period of time during which the value of an index is different from the inter-ictal and post-ictal values) and c) post-ictal (defined as the period of time during which the value of an index is different from inter-ictal and ictal values) is provided, in accordance with one illustrative embodiment. FIG. **14**B shows a seizure related metric **1403** in a two-threshold (**1405**/**1407**) graphical representation of two illustrative seizure events: **1401** and **1402**. The depicted seizure events **1401** and **1402** have ictal states **1482**A and **1482**B respectively and post-ictal states **1480**A and **1480**B respectively. In between seizure events **1401** and **1402** lie inter-ictal states **1483**A and **1483**B respectively. As illustrated, when the seizure related metric **1403** reaches/crosses the seizure threshold **1405** in an upward direction, the patient is said to be in an ictal state (**1482**A/**1482**B). When the seizure related metric **1403** reaches/crosses the post-ictal threshold **1407** in a downward direction, the patient is said to be in a post-ictal state (**1480**A/**1480**B) and when it crosses/reaches in an upward direction post-ictal threshold **1407** (without reaching/crossing ictal threshold **1405**), the patient is said to be in an inter-ictal state.

(159) FIG. **14**B also depicts an inter-seizure interval (ISI) **1410**A and **1410**B, as well as inter-post-ictal intervals **1481**A/**1481**B, for each illustrated seizure event **1401** and **1402** respectively, in accordance with one or more one embodiments. The illustrated ISI **1410**A may be defined as the time elapsed between the onset of two consecutive (or non-consecutive) seizures or ictal states and the ISI **1410**B may be defined as the time elapsed between the end of a seizure or ictal state and the onset of consecutive (or non-consecutive) seizures or ictal states, as shown in FIG. **14**B. An ISI may also be defined as the time elapsed between the end of a post-ictal state and the onset of consecutive (or non-consecutive) seizures or ictal states (shown as inter-ictal state **1483**A/**1483**B). Similarly, the illustrated inter-post-ictal intervals **1481**A may be defined as the time elapsed between the onset of two consecutive (or non-consecutive) post-ictal states and the inter-post-ictal intervals **1481**B may be defined as the time elapsed between the end of a post-ictal state and the onset of the next post-ictal state. The inter-ictal periods described herein are not exclusive, and other measures may be used as would be realized by one of ordinary skill in the art having the benefit of this disclosure.

(160) As illustrated, the ISI **1410**A has a shorter length than the ISI **1410**B. In other words, the ictal states **1482**A in seizure event **1401** are closer together in time than the ictal states **1482**B in seizure event **1402**. A shorter ISI may be an indication of a greater overall risk of having an extreme event and also of a higher burden and/or impact; progressive decrease (e.g., a trend) in ISI duration may be indicative of an increased risk for an extreme epileptic event/state. The longer the ISI (usually associated with longer inter-ictal periods) the greater the probability for recovery of body organs/systems to the inter-ictal state (baseline). The temporal length of ISIs may also be indicative of the overall probability of seizure occurrence. That is, in accordance with one or more embodiments, the longer the period between ictal states the lower the probability of a seizure

occurring in a patient (see FIG. **17**B below). In contrast, the shorter the ISIs, the higher the probability of a seizure occurring in a patient. The definitions of inter-ictal, ictal and post-ictal states apply to any and/or all autonomic, neurologic, metabolic, endocrine, tissue stress markers and quality of life indices. For example, heart rate, responsiveness/awareness, arterial pH, prolactin, CK, or quality of life during a seizure may be used to determine the onset and termination of the ictal and post-ictal states and the time of return to the inter-ictal state. This approach takes into account all patho-physiologic changes before the onset, during and following the termination to better track their "spatial" (referring to organs/systems spread) and temporal evolution, thus allowing the determination of each state according to each organ/system and each index.

(161) Additionally, an increase above a threshold (e.g., seizure threshold **1405**) may indicate an increased energy level in certain frequency bands related to a seizure event and/or extreme seizure event in a patient. A decrease below a threshold (e.g., post-ictal threshold **1407**) may indicate a decreased energy level in certain frequency bands related to a seizure event and/or extreme seizure event in a patient. It is noted that both increases and decreases in energy of various frequency bands related to seizure events and/or extreme seizure events in a patient may provide information related to a body organ from which the energy level/frequency band was recorded.

(162) Longer times spent in post-ictal states (e.g., **1480**A/**1480**B) typically may be the result of a more severe seizure, a decline in a patient's overall health or brain health, longer periods of unresponsiveness, an increased risk of injury, status epilepticus and/or SUDEP, and the like. Large magnitude crossings below the downward post-ictal threshold **1407** typically may indicate similar risks to the patient. Additionally, the time spent in post-ictal states (e.g., **1480**A/**1480**B) may be analyzed with and compared to the corresponding inter-seizure interval (ISI) and/or as inter-post-ictal intervals (e.g., **1481**A/**1481**B) of a seizure event to assess trends of seizure severity and/or intensity.

(163) In one embodiment, the post-ictal state (e.g., **1480**A/**1480**B) severity may be used to determine and warn of a risk of an extreme epileptic event/state. In an exemplary embodiment, a downward crossing of a post-ictal threshold **1407** representing the ninetieth percentile of post-ictal severity may indicate an increased risk of an extreme epileptic event/state requiring a warning and/or other treatment/response. It is contemplated that different percentile values may be used to set the downward crossing post-ictal threshold **1407**, and that the downward crossing post-ictal threshold **1407** may be adaptable. It is also contemplated that the thresholds **1405**/**1407** may be based upon a pre-determined or adaptable number of standard deviations of a normalized distribution of post-ictal severity of a patient. For example, if a value meets or exceeds three standard deviations from normal (i.e., the threshold may be seen as three standard deviations from normal), this may indicate that a warning of a risk/occurrence of an extreme epileptic state/event may be needed.

(164) Turning now to FIG. **15**, a temporal distribution of the probability of seizure occurrence before and after a seizure, in accordance with one embodiment, is depicted. FIG. **15** illustrates a relationship of the probability of seizure occurrence within a window of time relative to (around) an actual occurrence of a seizure. As indicated in FIG. **15**, for certain patients, there is an increased probability of seizure occurrence in the window beginning approximately 30 minutes prior to an actual occurrence of a seizure, and ending 30 minutes past the occurrence of the seizure. In other words, seizure occurrences in certain patients have a tendency to cluster with respect to time periods. In one embodiment, these clustering characteristics may provide for a quantitative statistical precursory diagnostic of impending seizures.

(165) Turning now to FIGS. **16**A and **16**B, a relationship between metrics (in this example between responsiveness/awareness (e.g., based on cognitive tests) and seizure severity determined for example using heart rate) is depicted for a non-extreme epileptic state/event (FIG. **16**A) and an extreme epileptic state/event (FIG. **16**B), in accordance with one embodiment. As shown in FIG.

16A, responsiveness/awareness, returns to its inter-ictal values before the next seizure. It should be noted that a recovery of responsiveness/awareness to baseline or inter-ictal levels in between seizures is associated with a low probability of extreme event/state occurrence. In contrast, FIG. **16**B depicts a seizure energy increasing to an extreme value (e.g., above the 90.sup.th percentile of seizure energy values for that patient), indicative of an extreme epileptic event (e.g., status epilepticus). Notice that responsiveness/awareness does not recover to inter-ictal levels before the next seizure which further depresses responsiveness.

(166) Turning now to FIGS. **16**C and **16**D, a relationship between responsiveness/awareness and inter-seizure interval (ISI) is depicted for a non-extreme epileptic state/event (FIG. **16**C) and an extreme epileptic state/event (FIG. **16**D), in accordance with one embodiment. As shown in FIG. **16**C, in a patient with relatively long ISI (i.e., infrequent seizure events) responsiveness/awareness recovers to inter-ictal levels before the next seizure. In contrast, FIG. **16**D depicts relatively short ISIs (i.e., closely temporally spaced seizures) resulting in an extreme epileptic event/state (e.g., a status epilepticus state) during which responsiveness/awareness remains below inter-ictal levels (i.e., at an impaired responsiveness/awareness value).

(167) Turning now to FIG. **17**A, a graphical representation of various seizure-related measures/dimensions (y-axis) with respect to time (x-axis) are depicted, in accordance with one or more embodiments. Seizure Severity Index (SSI) **1710** (the product of intensity and duration in this embodiment; extent of spread was not considered) may be determined in reference to the seizure threshold **1725** by calculating the time elapsed between the upward and downward crossings multiplied by the maximum of the curve, above the seizure threshold **1725**. Inter-seizure intervals may be calculated as the time elapsed between consecutive up-crossings of the seizure threshold or between a down-crossing of the seizure threshold **1725** and the next up-crossing. In addition to, or alternatively, any SSI, other indices such as responsiveness, awareness, kinetic data (e.g., body falls, limb direction, acceleration and trajectory), time spent in and magnitude of relative or absolute tachycardia (or bradycardia) hypoxia, lactic acidosis, and hypercortisolism respiratory failure, cardiac failure, pulmonary edema, cardiac arrhythmias, liver and/or renal failure, arterial hypertension, tissue hypercarbia and/or the like may be depicted. It should be noted that while only one seizure (the first) crosses the status epilepticus threshold **1720**, the figure represents an extreme epileptic state due in addition to the increasing progressive depression of responsiveness/awareness and the short ISIs.

(168) As a general matter, a patient's responsiveness and/or awareness, during and/or after an epileptic event or extreme epileptic event may be used as an indicator of epileptic event severity as well as a patient's health and/or disease state. A patient's responsiveness and/or awareness may be measured automatically using a variety of tests that rely on using audio, visual, olfactory or tactile signals to quantify its changes during the ictal and post-ictal periods compared inter-ictal. The responsiveness/awareness **1705** of a patient while not having seizures may be graphically viewed as a responsiveness baseline **1714**; the responsiveness/awareness crossed an impairment threshold **1715** in the downward direction during a seizure. That is, as responsiveness/awareness **1705** decreases, the impairment threshold **1715** may be reached or crossed. The responsiveness/awareness **1705** of the patient may be determined before, during and/or after a seizure event in order to determine the patient's responsiveness/awareness **1705**, the severity and/or intensity of a seizure event, a patient's risk of an extreme epileptic event/state and/or the like. That is, the more marked or longer a period of unresponsiveness, the more extreme the epileptic event or state, as discussed below with respect to FIG. **17**B.

(169) As depicted in FIG. **17**A, a seizure threshold **1725** and an extreme seizure event/state threshold **1720** may be set for a patient. The seizure threshold **1725** and the extreme event/state threshold **1720** may be based upon a reference to a non-extreme or to an extreme reference value(s) selected from one or more of the following: the body data collection module **275**, the physical fitness/integrity index unit **355**, the physical fitness/integrity determination unit **376**, the neurologic

index unit **510**, the autonomic index unit **520**, the endocrine index unit **540**, the metabolic index unit **542**, the tissue stress marker index unit **550**, the QOL unit **274**, the SSI unit **295**, the ISI unit **245**, the seizure burden unit **273**, the patient seizure impact unit **296**, the site(s) of seizure determination unit **293**, the seizure spread, duration and intensity determination unit **294**, the seizure (extreme seizure) ranking unit **247**, the seizure determination module **299**, seizure intensity ranking unit **1010**, seizure spread ranking unit **1015**, inter-seizure interval ranking unit **1025**, seizure duration determination unit **1030**, post-ictal determination unit **1033**, seizure impact ranking unit **1017**, seizure burden ranking unit **1018**, inter-seizure interval determination unit **1020**, seizure duration ranking unit, the extreme seizure event/state detection, quantification and risk determination unit **290** and/or the extreme epileptic event/state confirmation unit **287**. In one embodiment, an upward crossing of the seizure threshold **1720** by a seizure metric **1710** may indicate that a patient is having an extreme seizure event. In accordance with one embodiment, a downward crossing of a threshold **1730** by the seizure metric **1710** is indicative of it entering the post-ictal energy zone state **1740** associated with decreased responsiveness/awareness **1705** with complex partial or generalized seizures. As shown in FIG. **17**A, successive seizure events and/or extreme seizure events (indicated by the upward crossings of the status threshold **1720** and/or the seizure threshold **1725**) are associated in this embodiment with increasing impairment of responsiveness/awareness **1705**.

(170) Turning now to FIG. **17**B, a graphical representation of conditional (compared to the unconditional) probability of seizure occurrence as a function of time elapsed from the last seizure event, is depicted according to one or more embodiments. As shown, the longer the time elapsed from the last seizure, the longer the time to the next seizure and vice-versa. The shorter the ISI between events, the more probable that the brain is approaching an extreme epileptic state or is already in such a state. The solid curve is representative of the conditional probability, and the dashed line is representative of the unconditional.

(171) Turning now to FIG. **18**, a stylized graphical representation of inter-relations of epilepsy as a disease with its symptoms of and effects on patients is provided, in accordance with one or more embodiments. In one embodiment, the disease is epilepsy. Pharmaco-resistant seizures are associated with an increase in mortality and morbidity rates (compared to the general population and to epilepticus whose seizures are controlled by medications), eventual impairment of cognitive functions and mental health, and markedly degraded quality of life for patients and their families. Seizures may impair motor control, responsiveness to a wide class of stimuli, and other cognitive functions. Certain pharmacological agents used for treatment of epilepsy cause osteoporosis, reproductive dysfunction, liver and bone marrow damage, and in rare cases, death. FIG. **18** depicts relationships between epilepsy and some of its comorbidities, with the directionality of each arrow indicating an amplifying effect. For example, at exemplified in FIG. **18**, seizures enhance epilepsy (and/or vice versa), which can lead to bodily injuries and/or head injuries which in turn may lead to other problems, such as cognitive deficits, depression, decreased social activity and decreased quality of life. Moreover, extreme events/state can lead to neurological sequelae, multiple organ failures, and to an increased risk of death.

(172) In one embodiment, identifying an extreme seizure event in a patient may be performed by examining a body index that is affected by a first seizure event. If the change in the body index caused by a seizure does not return to within a range of reference values prior to the occurrence of a second seizure, in one embodiment, this would be indicative of an extreme seizure event. For example, if the heart rate of the patient rises during a first seizure, and the heart rate remains above reference values by the time a second seizure occurs, this seizure is classified as extreme even if the ISI interval duration is within a range of non-extreme reference values for that patient. In this case, the MD **200** may take one or more actions in response to the extreme seizure event, such as issuing a warning (e.g., to a patient, care giver(s) and/or emergency responders), categorizing the event, logging the event, providing therapy(ies), etc. Providing a therapy may include providing an

electrical therapy, a chemical therapy, a thermal therapy, a supportive treatment, etc., for treating the seizure event and the changes it causes in body signals. In one embodiment, providing the supportive treatment may include at least one of providing fluids, providing tracheal intubation, providing body cooling, providing brain cooling, providing oxygen, or providing non-seizure drugs. In another embodiment, a seizure may be classified and managed as an extreme event if the seizure occurs in the context of a body signal change not caused by a seizure. For example, a patient has a diagnosis of epilepsy and of cardiac arrhythmia and neither is the cause of the other, that is, they are etiologically unrelated; any seizure that occurs when the patient is having an arrhythmia, would be classified and managed as an extreme event. If a patient with generalized tonic-clonic seizures also has asthma and a seizure occurs during an asthma attack this seizure could be classified and managed as an extreme event.

(173) Turning now to FIG. **19**, a stylized depiction of an exemplary body index chart, in accordance with one embodiment, is illustrated. For ease of discussion, the body index value relating to FIG. **19** is described in terms of heart rate; however, the concepts relating to FIG. **19** would apply to a variety of body index values.

(174) Prior to the occurrence of a first seizure event, heart rate values for a patient may be within a range of body index reference values indicated by an upper body index reference boundary **1920***a*, and a lower body index reference boundary **1920***b*. The range of body index reference values **1920***a*, **1920***b* generally relates to an inter-ictal region, as shown in FIG. **19**. After the occurrence of the first seizure event, heart rate signals **1910** may rise and fall in the ictal region, as exemplified in FIG. **19**. A dashed-line curve representing the median response of the change in the patient's ictal heart rate (**1940**), is shown in FIG. **19**. In time, after the end of the seizure, the heart rate of the patient may generally return to reference values **1920** (inter-ictal region). In one embodiment, deviations from the median change in ictal heart rate **1940** (as determined from a multiplicity of seizure events) may be determined in order to establish whether or not an extreme seizure event has occurred. In one or more embodiments, seizures of similar duration may be compared, a multiplicity of seizures may be normalized and compared, a time warping function may be applied to one or more seizures for comparison of the one or more seizures.

(175) Continuing referring to FIG. **19** as an example, changes in heart rate outside an X.sup.th percentile (e.g., **1950**) and a Y.sup.th percentile (e.g., **1960**) changes in heart rate that occur as a result of the first seizure event may be used to determine whether an extreme seizure event has occurred. In one embodiment, the X.sup.th percentile may represent the 95.sup.th percentile, or alternatively, various other percentiles (e.g., 90.sup.th, 85.sup.th, 80.sup.th, 75.sup.th, 70.sup.th, 65.sup.th, 60.sup.th, 55.sup.th, 50.sup.th, etc.). Similarly, in one embodiment, the Y.sup.th percentile may represent the 5.sup.th percentile, or alternatively, various other percentiles (e.g., 10.sup.th, 15.sup.th, 20.sup.th, 25.sup.th, 30.sup.th, 35.sup.th, 40.sup.th, 45.sup.th, 50.sup.th, etc.).

(176) Turning now to FIG. **20**, a stylized depiction of a body index chart showing an outlier heart rate change, in accordance with one embodiment, is illustrated. As an example, after the occurrence of a first seizure event, a patient's heart rate changes may be above the 95.sup.th percentile **1950**. An outlier heart rate signal **1970** that rises above the X.sup.th percentile change in heart rate **1950** may be determined. Moreover, in one embodiment, if the value of the outlier heart rate signal **1970** exceeds the X.sup.th percentile (e.g., 95.sup.th percentile in this example) change in heart rate **1950** by a predetermined distance (outlier distance from the X.sup.th percentile **1955**), may indicate an increased probability that the next epileptic event may also be extreme, and that a high-risk time period (to the next epileptic event) is deemed to have been entered. The high-risk time period may refer to an elevated risk of an extreme seizure event occurring before a patient returns to an inter-ictal state. In one embodiment, when the high-risk time period is entered, one or more actions (e.g., issuing a warning, delivering a therapy, logging, disabling a vehicle or power equipment, etc.) may be performed. Further, one or more counter(s) may be used to maintain a count of high-risk time periods, as well as a log of time periods defined by the beginning of a high risk time period, until a

subsequent seizure. The log may also include time of day of the high risk time period, patient body index data, etc. Such logged information may be used to estimate the time of onset of an extreme event.

(177) In one embodiment, if a second seizure event occurs prior to the detected change in heart rate returning to the inter-ictal range (within the body index reference values **1920**), a determination that an extreme seizure condition is occurring or has occurred may be made.

(178) In an alternative embodiment, when the second seizure event is detected, the SSI value of the second seizure event is compared to a reference SSI value. If the SSI value of the second seizure event is greater than a reference SSI value, a determination that an extreme seizure condition is occurring or has occurred may be made.

(179) The recovery time(s) of a body index relative to a subsequent seizure event may provide an indication of an extreme seizure event. In one embodiment, various body index data may be collected for each patient, and reference body index value(s) for a particular patient may be determined. Further, reference body index values for groups or types of patients, seizures (e.g., partial or generalized) or epilepsy (e.g., symptomatic or idiopathic) may be determined A database for storing various categories of body index data may be provided. This database may be used by the MD **200** to perform the assessment of extreme seizure events described herein. In addition to comparing the body index response to a reference body index, comparison of the body index response may also include comparing the morphology of body index response to a predetermined morphology reference.

(180) In one embodiment, one or more actions may be performed upon a determination that an extreme seizure event has occurred, including but not limited to issuing warning, logging, providing therapy, informing medical personal, disabling one of more devices/machinery (e.g., an electric saw being operated by a patient), etc. Further, the extreme seizure event may be ranked as a result of determining that the change in the detected body signal was above a first threshold (or below a first threshold) when the second seizure event occurred. Similarly, the extreme seizure event may be ranked as a result of determining that the change in the detected body signal was above a second threshold (or below a second threshold) when the second seizure event occurred. In one embodiment, the first ranking is higher than the second ranking.

(181) Similar analysis may be performed on other types of body signals, such as, but not limited to, heart activity, respiratory activity, blood pressure, body temperature, blood gas concentrations, and/or ECoG. Turning now to FIG. **21**, a stylized depiction of a body signal energy chart (e.g., ECoG), in accordance with one embodiment, is illustrated.

(182) FIG. **21** illustrates a median body signal energy change (e.g., for an ECOG signal) (**2110**). The median body signal energy **2110** may increase from a range of reference signal energy values defined by the upper and lower body signal energy boundaries **2120***a*, **2120***b* (i.e., inter-ictal region) to the ictal region, and when the seizure ends, may enter the post-ictal region (e.g., below the reference body signal energy value **2120***b*). It should be noted in FIG. **21** that the body signal energy generally passes transiently through the inter-ictal region and into the post-ictal region. Relative to the median body signal ictal energy change **2110**, a response representing an X.sup.th percentile change in body signal energy value **2150** and a Y.sup.th percentile change in body signal post-ictal energy value **2140** may be determined (as illustrated in FIG. **21**). In one embodiment, the X.sup.th percentile may represent the 95.sup.th percentile, or alternatively, various other percentiles (e.g., 90.sup.th, 85.sup.th, 80.sup.th, 75.sup.th, 70.sup.th, 65.sup.th, 60.sup.th, 55.sup.th, 50.sup.th, etc.). Similarly, in one embodiment, the Y.sup.th percentile may represent the 5.sup.th percentile, or alternatively, various other percentiles (e.g., 10.sup.th, 15.sup.th, 20.sup.th, 25.sup.th, 30.sup.th, 35.sup.th, 40.sup.th, 45.sup.th, 50.sup.th, etc.).) Moreover, an outlier body signal energy value **2180** may be tracked relative to the X.sup.th percentile change in body signal energy value **2150** and the Y.sup.th percentile change in body signal energy value **2140**. It should be noted that other measures of central tendency, e.g., mean, quartiles, etc., or other statistical measures may be used

instead of, or in addition to, the median values exemplarily depicted in FIGS. **19-22** and as described herein.

(183) In one embodiment, a determination may be made as to whether an outlier body signal energy value (**2180**) is above an X.sup.th percentile by a predetermined margin, i.e., an outlier distance above (**2170**) an X.sup.th percentile. Upon an affirmative determination based upon this inquiry, a determination may be made that an extreme seizure event is occurring or is imminent. Similarly, a determination may be made as to whether an outlier body signal energy value (**2170**) is below an Y.sup.th percentile by a predetermined margin, i.e., an outlier distance below (**2140**) a Y.sup.th percentile. Upon an affirmative determination based upon this inquiry, a determination may be made that an extreme seizure event is occurring or is imminent. In one embodiment, one or more action may be performed upon a determination that an extreme seizure event has occurred or is imminent, including but not limited to issuing warning, logging, providing therapy, informing medical personal, disabling one of more equipment operation, automobile, machinery, etc. In some embodiments, an extreme seizure event may be declared regardless of ISI and/or SSI values if a seizure occurs while the seizure burden and/or patient impact have not returned to inter-ictal values. For example, a subject falls during a seizure and suffers a brain contusion as a result of this. Any seizure that occurs within the period of time before the contusion clears (e.g., six weeks) may be declared as extreme regardless of SSI values and/or ISI values based for example, upon the patient's health.

(184) In addition to comparing the detected body signal energy response to reference or median energy signal values, comparison of the body signal energy response may include comparing the morphology of the body signal energy response to a predetermined morphology. In another embodiment, the rate of change (increase or decrease) instead of the magnitude of the change in a body signal may be used to determine of an event is extreme.

(185) Turning now to FIG. **22**, an exemplary, stylized depiction of various time periods within distributions (in percentiles) of values of an exemplary body index chart, during the inter-ictal, ictal and postictal periods, is illustrated. As described above, when a second seizure event occurs prior to the time period when the change in body index returns back to the inter-ictal range (**1920***a*, **1920***b*), an extreme seizure event is deemed to have occurred. In one embodiment, extreme seizure events may be further granulized or ranked. The ranking may, for example be based upon the particular time within the ictal time period of the first seizure at which the second seizure occurs. FIG. **22** illustrates various time markers (Time-A through Time-F) that can be used to rank extreme seizure events and the ranking may be performed, for example, by determining the time at which the second seizure occurred relative to the onset of the first seizure, the SSI percentile value of the first seizure at the onset of the second seizure, and for a given percentile value of the first seizure, whether the second seizure occurs near the onset (Time-A), near the peak (Time-C) or near the end (Time-F) of the seizure. For example, if a second seizure occurs at Time-C during a first seizure with an SSI in the 95.sup.th percentile, this second seizure will be ranked higher than if the second seizure had occurred at Time-A. Additionally, a second seizure occurring at Time-B may be ranked as more extreme if the SSI value of the first seizure is in the 50.sup.th percentile than if it is in the 5.sup.th percentile. In this manner, extreme seizure events can be ranked from less to more extreme) based upon time of occurrence of the second seizure (within the ictal period of the first seizure) and/or its SSI value.

(186) In alternative embodiments, in addition to the ISI and SSI determinations described above, other indices may be used to determine whether an extreme seizure event has taken place or is imminent. For example, pathologic high frequency brain wave oscillations may be used as an indicator that an extreme seizure event has taken place or is imminent. In one embodiment, pathologic high frequency oscillations may be defined as neuronal/neuropil oscillations with a frequency of approximately 80 Hz or higher.

(187) Other exemplary markers used to determine whether an extreme seizure event has taken

place or is imminent may be based upon analysis of epileptiform discharge(s), electrodecremental response(s), and electrographic seizures. An electrographic seizure may refer to a sub-clinical seizure that is generally only detectable using EEG or other electrical measurements. In one embodiment, after a threshold number (e.g., two seizures within an ISI below the 20.sup.th percentile of a distribution of an ISI value) of electrographic seizures have occurred within a predetermined time period, a determination may be made whether an extreme seizure event has taken place or is imminent. Further, electrodecremental response may refer to sudden transient decreases in the amplitude of background EEG rhythms (e.g., recorded using conventional filter settings such as 1 Hz and 70 Hz) associated with the appearance of behavioral activity indicative of seizures. In one embodiment, transient decreases in the amplitude of background EEG rhythms and/or appearance of activity indicative of seizures (e.g., seizure activity detected by sensors such as an accelerometer, inclinometer, sound detector, etc.) may be used to determine whether an extreme seizure event has taken place or is imminent. Moreover, epileptiform discharge may refer to brain shape, e.g., sharply contoured brain wave(s) with a duration of about up to 200 ms, that may or may not form complexes with slow waves (e.g., 1-4 Hz). In one embodiment, the duration of the epileptiform discharge, site of origin, and/or the shape, e.g., sharpness of the brain waves may be used to determine whether an extreme seizure event is imminent, is taking place, or has taken place.

(188) Some exemplary embodiments of the present disclosure are described below in paragraphs I. through V. I. In one embodiment, the present disclosure provides a method for identifying an extreme seizure event in a patient. The method includes identifying at least two seizure events; determining at least one inter-seizure interval (ISI) value related to said at least two seizure events; comparing said determined at least one ISI value to at least one reference value; and identifying an occurrence of an extreme seizure event, based upon the comparison of said determined ISI value to said at least one reference value. II. In one embodiment, detecting said first seizure described in paragraph I. above comprises detecting an epileptic seizure having an SSI value exceeding a first SSI threshold, and wherein detecting said second seizure comprises detecting an epileptic seizure having an SSI exceeding a second SSI threshold. III. In another embodiment, the present disclosure provides a method for identifying an extreme seizure event in a patient. The method includes identifying a first seizure event of a first type and a second seizure event of the first type; identifying a third seizure event of a second type and a fourth seizure event of the second type; determining a first inter-seizure interval (ISI) value between said first and said second seizures; determining a second inter-seizure interval (ISI) value between said third and fourth seizures; performing a first comparison of said determined first ISI value to at least a first reference value; performing a second comparison of said determined second ISI value to at least a second reference value; and identifying an occurrence of an extreme seizure event, based upon at least the first or the second comparisons. IV. In another embodiment, the present disclosure provides a medical device and/or a medical device system that comprise one or more controllers, hardware module, software module, and/or firmware module capable of performing the steps described in paragraph I above. V. In another embodiment, the present disclosure provides a medical device and/or a medical device system that comprise one or more controllers, hardware module, software module, and/or firmware module capable of performing the steps described in paragraph III above.

(189) The methods and apparatuses disclosed and claimed herein may be made and executed without undue experimentation in light of the present disclosure. While the methods and apparatus of embodiments of this invention have been described in terms of particular embodiments, it will be apparent to those skilled in the art that variations may be applied to the methods and apparatus and in the steps, or in the sequence of steps, of the method described herein without departing from the concept, spirit, and scope of the invention, as defined by the appended claims. It should be especially apparent that the principles of the invention may be applied to selected cranial nerves other than, or in addition to, the vagus nerve to achieve particular results in treating patients having

epilepsy, depression, or other medical conditions.

(190) The particular embodiments disclosed above are illustrative only as the invention may be modified and practiced in different but equivalent manners apparent to those skilled in the art having the benefit of the teachings herein. Furthermore, no limitations are intended to the details of construction or design herein shown other than as described in the claims below. It is, therefore, evident that the particular embodiments disclosed above may be altered or modified and all such variations are considered within the scope and spirit of the invention. Accordingly, the protection sought herein is as set forth in the claims below.

Claims

1. A non-transitive computer readable program storage device encoded with instructions that, when executed by a computer, performs a method via one or more processors for identifying an extreme seizure event in a patient, comprising: collecting body data from the patient using an electrical sensor; identifying a first seizure event and a second seizure event from the collected body data; determining a first inter-seizure interval value related to the first seizure event and a second inter-seizure interval value relating to the second seizure event; comparing the determined of the first inter-seizure interval value and the second inter-seizure interval value to a population of patients; determining a first severity of the first seizure event and a second severity of the second seizure event; comparing the first severity and the second severity to the population of patients; identifying an occurrence of the extreme seizure event based on the comparison of the first severity and the second severity to the population of patients; setting a first flag indicative of the extreme seizure event; providing a signal indicative of the extreme seizure event; issuing a warning notice; ranking the extreme seizure events; initiating a logging sequence of the extreme seizure events; initiating a reporting sequence for the extreme seizure events; in response to the detection of the extreme seizure event, delivering at least one of an electrical therapy, a drug therapy, a thermal therapy, and an oxygen therapy; determining after delivery of the therapy, the impact of the extreme seizure event on the patient; and storing: a time elapsed between at least one of a plurality of extreme or non-extreme seizure events and the identifying of the extreme seizure event; differences in ranking between the identified extreme seizure event and: a plurality of extreme seizure events; a plurality of non-extreme seizure events; the therapies used; one or more parameters of the therapy used; an effect of the therapy on the extreme seizure event; a time at which the extreme seizure event was terminated; a clinical outcome of the patient following the extreme seizure event; a signal indicative of at least one of a time of day, a time of month, or a time of year; whether the patient was awake or asleep at the time of the occurrence of the extreme seizure event; a sleep stage of the patient at the time of the occurrence of the extreme seizure event.

2. The non-transitive computer readable program storage device of claim 1, wherein the logging sequence of the method further comprises at least one of: storing at least one of a start time of the extreme seizure event, an end time of the extreme seizure event, a duration of the extreme seizure event, a time and a date of the extreme event, a time of providing the therapies, and a time of issuing the warning notice into a memory of at least one medical device; and whether the patient was in a physical or cognitive sedentary state or active state wherein the physical or cognitive sedentary state includes at least one of a resting state or a mentally relaxing state, and wherein the active state includes at least one of the patient being physically and/or mentally active.

3. The non-transitive computer readable program storage device of claim 1, wherein providing the therapy comprises providing at least one of: an electrical therapy, a chemical therapy, or a thermal therapy; or a supportive treatment comprising at least one of: providing fluids, providing tracheal intubation, providing body cooling, providing brain cooling, providing oxygen, or providing non-seizure drugs; and wherein issuing the warning notice in the method indicates the increased risk to the health and/or the safety of the patient comprises emitting a sound, a light or a vibration to

caregivers, or activating at least one of a notification to an emergency responder or a remote device to a care provider station.

4. The non-transitive computer readable program storage device of claim 1, wherein the method further comprising: requesting an extreme seizure event confirmation of the identifying the occurrence of the extreme seizure event; receiving a response to the requesting; and performing at least one of: setting a second flag confirming the extreme seizure event if the response to the requesting indicates that the patient is having the extreme seizure event; deactivating the first flag if the response indicates that the patient is not having the extreme seizure event; cancelling at least one of the warning or the therapy in response to the deactivation; logging an event as a false event or an unconfirmed event; notifying at least one of the patient, a caregiver or an emergency responder that the warning notice was in response to the false event or the unconfirmed event; or storing a signal indicative of at least one of: a time of day, a time of month, or a time of year of the false event; or whether the patient was awake or asleep at the time of the occurrence of the false event, and if the patient was a wake whether the patient was in a physical or cognitive sedentary state or active state wherein the physical or cognitive sedentary state includes at least one of a resting state or a mentally relaxing state, and wherein the active state includes at least one of the patient being physically and/or mentally active; wherein when the patient is in the sleep condition collecting data relating to a stage of sleep.

5. The non-transitive computer readable program storage device of claim 1, wherein the method further comprising determining a time spent in the extreme seizure event.

6. The non-transitive computer readable program storage device of claim 1, wherein the method further comprising identifying a pathophysiological effect of the extreme seizure event selected from a group consisting of: damage to brain tissue resulting in permanent or serious motor, visual, sensory, or cognitive skills; a respiratory failure; a respiratory distress syndrome; a pulmonary edema; a cardiac arrhythmia, a cardiac failure, an arterial hypertension or an arterial hypotension; a metabolic acidosis; a liver failure or a renal failure; one or more bone fractures; one or more skin abrasions; one or more bruises, wounds or burns; or an organ failure.

7. The non-transitive computer readable program storage device of claim 1, wherein an onset and a termination of an ictal period or of the post-ictal period is determined in the method using at least one of a neurologic index selected from brain energy, a level of consciousness, complex reaction response times, and a kinetic activity, or an autonomic index selected from a heart rate, a heart rate variability, a cardiac cycle morphology, a respiratory rate, a tidal volume, a respiratory cycle morphology, an oxygen saturation, and an end tidal CO_2.

8. The non-transitive computer readable program storage device of claim 1, wherein the method further comprises: determining a risk of death in response to identifying the occurrence of the extreme seizure event, wherein determining the risk comprises determining: a decreasing heart rate variability (HRV); an ST complex elevation; an ST complex depression; an QT elongation; a multi-focal premature ventricular contraction (PVC); a ventricular tachycardia; a ventricular fibrillation; a pulmonary hypertension; an arterial hypotension; or a respiratory distress syndrome; issuing a risk warning of the risk of death in response to determining the risk of death; and increasing the provided therapy in response to determining the risk of death.

9. The non-transitive computer readable program storage device of claim 1, wherein a state of a patient's overall health and a body state are determined in response to a seizure severity index exceeding a reference value.