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Brain burst suppression activity

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Abstract

There is robust clinical and experimental evidence in humans and in animals of an electroencephalographic pattern known as burst suppression (BSP); this is characterized by epochs of very low amplitude followed by bursts of high amplitude. Such a feature is observed on the electroencephalogram trace from individuals under various pathological but also physiological conditions; thus, several studies have searched for the physiological meaning and neuronal generator of the BSP. In this review we summarize the knowledge obtained worldwide on this topic, which provides important insights for sleep, anesthesia, and neuroscience research. **Keywords**: burst suppression, EEG, isoelectric, anesthesia, consciousness.

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Introduction

A brain electrical activity trace characterized by epochs of very low amplitude followed by bursts of high amplitude in the electroencephalogram (EEG) is known as burst suppression pattern (BSP) (Fig. 1). This pattern was first described in 1949 in dogs anesthetized with amobarbital (Swank & Watson, 1949) and since then it has been observed under various physiological and pathological conditions, which will be discussed forward. In an anesthetized patient, as anesthetic concentration gets higher the EEG waves get progressively slower until BSP appears at deeper stages (Antunes, Roughan, & Flecknell, 2003; K. Hartikainen, Rorarius, Mäkelä, Yli-Hankala, & Jäntti, 1995; Rampil, 1998; Rampil et al., 1988; Silva, Ferreira, Venâncio, Souza, & Antunes, 2011). The duration and number of BSP episodes increases as anesthesia deepens (Jang, Choi, & Lee, 2009). Suppression periods have a quasi-periodic nature when anesthesia conditions are stable (Brenner, 1985). But as anesthetic drug concentration gets higher, the proportion of flat EEG periods increases until EEG silence is eventually reached (Koitabashi, Ouchi, & Umemura, 2004; Lukatch, Kiddoo, & Maciver, 2005; Rampil & Laster, 1992; Vijn & Sneyd, 1998; Yoshitani, Kawaguchi, Takahashi, Kitaguchi, & Furuya, 2003). In this review we summarize the knowledge regarding BSP, its mechanisms and characteristics.

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Electrophysiological features of BSP

The electrophysiological features of BSP have been described by several authors based on the amplitude and the predominant frequencies on the EEG trace. During suppression periods of the BSP the dominant frequency is δ (0.5–3.5 Hz), with almost no power in others bands (Joutsen et al., 2009). Suppression is clearly observed as broadband reductions in power in the spectrogram (Ching, Purdon, Vijayan, Kopell, & Brown, 2012). During bursts there are δ or θ waves or both (0.5–3.5 and 3.5–7.5 Hz), intermixed with faster waves of mixed α (7.5–12.5Hz) and β (12.5–30Hz) waves (Aminoff, 1999; E. Niedermeyer, Sherman, Geocadin, Hansen, & Hanley, 1999; Raith, Steinberg, & Fischer, 2010) (Figure 2). However, it must be kept in mind that electrophysiological features of BSP may vary according to the anesthetic drug used (Akrawi, Drummond, Kalkman, & Patel, 1996). The amplitude of the BSP varies considerably between bursts and suppression periods. During suppression there is isoelectricity or low voltage, which is usually lower than 20 μV, while during burst periods the voltage is normal to high (≥50 μV) (Jang et al., 2009; Joutsen et al., 2009; Noachtar et al., 1999; Rundgren, Westhall, Cronberg, Rosén, & Friberg, 2010; Silva, Campos, et al., 2011).

BSP function

Although a function has not been clearly elucidated, there is evidence and biological plausibility suggesting BSP as a state of optimization of brain energy (Ching et al., 2012). This is supported by some facts. Etiologies that produce BSP have in common that they decrease cerebral metabolism (De Rubeis & Young, 2001; Ferron, Kroeger, Chever, & Amzica, 2009; Kroeger &

Figure 1. BSP. Rat electroencephalogram recording under 2% isoflurane anesthesia.

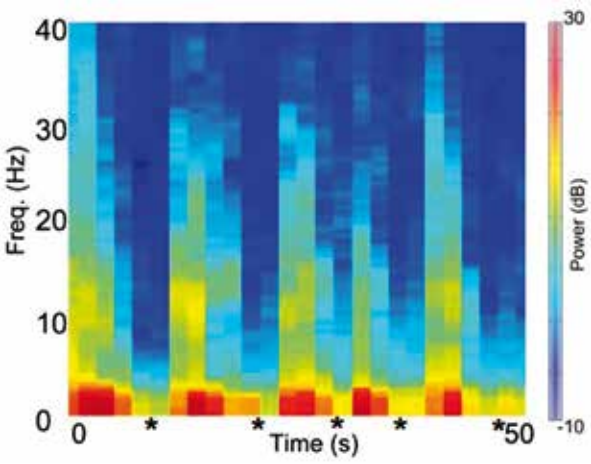

Figure 2. Spectrogram of a typical BSP obtained from a human anesthetized with propofol. Note the suppression periods (*) as temporal power reductions in all frequency bands. (Figure modified from Ching S, Purdon PL, Vijayan S, Kopell NJ, Brown EN. A neurophysiological-metabolic model for burst suppression. Proc Natl Acad Sci U S A 2012;109(8):3095-100).

Amzica, 2007; Michenfelder & Milde, 1991; Ohtahara & Yamatogi, 2003; Ostermann, Young, Sibbald, & Nicolle, 2000; Pagni & Courjon, 1964; Weissenborn, Wilkens, Hausmann, & Degen, 1991), whereas anesthetics associated with increased cerebral metabolic rate of oxygen consumption, such as ketamine, do not produce BSP (Barash, 2009), suggesting a link between reduced cerebral metabolism and this EEG pattern. Additionally, anesthesia-induced BSP has been shown to have neuro-protective effects that could be achieved through reducing brain metabolism (Doyle & Matta, 1999). Last, BSP is a surrogate marker for increased risk of death in sedated critically ill patients (Watson et al., 2008) because they probably have major brain compromise.

Anesthetics and BSP

Some drugs used as anesthetics induce BSP, whereas others do not; table No. 1 (Ambrisko, Johnson, & Chambers, 2011; Bo, Soragna, Specchia, Chimento, & Favalli, 2003; Bruhn, Bouillon, & Shafer, 2001; Fitch, McGeorge, & MacKenzie, 1978; Haga, Tevik, & Moerch, 2002; Johnson & Taylor, 1998; Mandema, Kuck, & Danhof, 1992; Modica & Tempelhoff, 1992; Nunes, Cavalcante, & Franco, 2011; Pan, Chen, Lai, & Luoh, 1994; Prior, Maynard, & Brierley, 1978; Rampil et al., 1988; Saady & Hicks, 1980; Sellers, Carr, Bernstein, Sellers, & Koch-Weser, 1972; Soehle et al., 2010; Theilen et al., 2000; van der Linde et al., 2011; Van Ness, 1990; Walling & Hicks, 2006) and No. 2 (Johnson & Taylor, 1998; Nunes et al., 2011; Sebel, Bovill, Wauquier, & Rog, 1981), respectively. BSP varies considerably depending on the anesthetic doses (Bruhn et al., 2001; Ferron et al., 2009; Luo & Leung, 2009; MacKay, Sleigh, Voss, & Barnard, 2010; Soehle et al., 2010; Van Ness, 1990). However, a study showed that the amount of BSP in anesthetized patients is not strongly correlated to the calculated effect-site concentration of fentanyl, propofol or desflurane (MacKay et al., 2010). This could also be the case for other drugs. Likewise, electrophysiological parameters of the BSP may vary according to the anesthetic drug used (Akrawi et al., 1996). For instance, propofol BSP varies considerably compared to BSP induced by volatile agents; their main differences are summarized in Table 3 (Akrawi et al., 1996; Besch et al., 2011; Ferenets et al., 2006; K. Hartikainen et al., 1995; Jäntti, Yli-Hankala, Baer, & Porkkala, 1993; Silva, Campos, et al., 2011; Wolter et al., 2006).

Table 1. Drugs that can induce a BSP at sufficient doses.

Medications known to induce a BSP
Barbiturates
Propofol
Etomidate
Halogenated ethers
Alfaxalone/alfadolone (Althesin)
Chloral hydrate
Midazolam
Halothane-alfaxalone
Diethyl ether

Table 2. Drugs that do not induce a BSP even at their highest doses.

Medications unable to induce a BSP
Halothane
Fentanyl
Ketamine

Table 3. Main differences among propofol BSP and volatile agents BSP.

Propofol BSP	Volatile agents BSP
Smoother wave forms	More abrupt changes in direct current level
Shorter duration	Longer duration
Lower amplitude	Higher amplitude
13-15 Hz spindle activity	No spindle activity

BSP and anesthetic monitoring

There are several EEG-based algorithms designed to measure anesthetic depth. Some of the most used spectral parameters (SP) and indices used to monitor anesthetic depth are shown in Table 4. The algorithms of each of them are beyond the goals of this manuscript and readers should refer to the following references for more information (Greene, Benson, Tranquilli, & Grimm, 2004; Jensen, Jospin, Gambus, Vallverdu, & Caminal, 2008; S. Kreuer et al., 2008; Sascha Kreuer & Wilhelm, 2006; Morimoto et al., 2004; Revuelta et al., 2008; Riker, Fraser, & Wilkins, 2003; Silva, Campos, et al., 2011; Silva, Cardoso-Cruz, Silva, Galhardo, & Antunes, 2010; Silva, Ferreira, et al., 2011; van der Linde et al., 2011).

Several authors have assessed the performance of different EEG-derived parameters to detect anesthetic dose used and anesthetic plasma concentration (Silva, Campos, et al., 2011; Silva et al., 2010; Silva, Ferreira, et al., 2011). All of them have found better correlation coefficients when a BSP correction factor is added to the algorithm of the SP as follows: BSP corrected SP = SP × (1 – BS/100) where BS represents the suppression periods of the BSP . With the exception of approximate entropy (Anier, Lipping, Jantti, Puumala, & Huotari, 2010; Bruhn, Röpcke, Rehberg, Bouillon, & Hoeft, 2000; Ihmsen et al., 2008), spectral parameters have problems to detect BSP because of a tendency to increase when it appears (D. Li, Li, Liang, Voss, & Sleigh, 2010; X. Li, Cui, & Voss, 2008; Olofsen, Sleigh, & Dahan, 2008; Rampil, 1998; Silva, Ferreira, et al., 2011). This paradoxical increase is attributed to the high-frequency components of BSP (Antunes, Golledge, Roughan, & Flecknell, 2003; Ihmsen et al., 2008; X. Li et al., 2008; Schwender et al., 1996; Silva et al., 2010) and disappears when a correction factor for BSP is applied (Silva et al., 2010). Thus, BSP seems to be an indispensible component for a good anesthetic-depth parameter, especially when deep anesthetic states are expected. Likewise, it is well known that indices such as BIS, NTindex and IoC include the percentage of suppression periods in the BSP EEG (known as burst suppression ratio or BSR) in their algorithms (Baulig, Seifert, Schmid, & Schwarz, 2010; Bruhn, Bouillon, & Shafer, 2000; Jensen et al., 2008; Sascha Kreuer & Wilhelm, 2006; Musialowicz et al., 2010; Revuelta et al., 2008; van der Linde et al., 2011), although the weight of BSP for each of these indices is variable. Also, computation of the power spectrum using long EEG epochs will produce distortion of burst-suppression activity (Levy, 1984).

Table 4. Spectral parameters and indices used to monitor anesthetic depth.

Spectral parameters	Single-scale permutation entropy Composite multi-scale permutation entropy Approximate entropy Median edge frequency Spectral edge frequency 95%
Indices	Bispectral index (BIS) Index of consciousness (IoC) Narcotrend index (NTindex)

BSP not related to anesthesia

A BSP not only appears under the effect of anesthetics; it has also been reported in comatose patients after traumatic brain injury, hypoglycemic coma, hypoxemia, vascular brain injury, cases of overdose of drugs that depress central nervous system activity, profound hypothermia, anoxic-ischemic encephalopathy after cardio-respiratory arrest, patients with any severe diffuse encephalopathy, and during any stage of neonatal sleep (De Rubeis & Young, 2001; Declerck, Liu, Chazot, & Fischler, 2009; Hayashida et al., 2007; Johansen, 2001; Levy, Pantin, Mehta, & McGarvey, 2003; N. Liu, Chazot, Mutter, & Fischler, 2006; Marion et al., 1997; Michenfelder & Milde, 1991; Myles & Cairo, 2004; Nakashima, Todd, & Warner, 1995; Ernst Niedermeyer & Lopes Da Silva, 2005; E. Niedermeyer et al., 1999; Ostermann et al., 2000; Pagni & Courjon, 1964; Püttgen & Geocadin, 2007; Savard & Huot, 2008; Schutz, Struys, Sinclair, & Stockler, 2011; Schutz, Wong, O'Kusky, Innis, & Stockler, 2011; Seder, Fraser, Robbins, Libby, & Riker, 2010; Stecker, 2007; Stecker et al., 2001b; Umegaki et al., 2003; Weissenborn et al., 1991; Young, 2000). Also, BSP has been associated with brain death (Escudero et al., 2005; Misis, Raxach, Molto, Vega, & Rico, 2008; Vivien, Langeron, & Riou, 2007; Vivien et al., 2002).

BSP as a marker of poor prognosis after brain injury

There is considerable evidence associating BSP after cardiac or respiratory arrest with poor outcome and high mortality (Bassetti, Bomio, Mathis, & Hess, 1996; Borges, Botós, Bastos, Godoy, & Marchi, 2010; Hockaday, Potts, Epstein, Bonazzi, & Schwab, 1965; Kawai, Thapalia, & Verma, 2011; Püttgen & Geocadin, 2007; Rossetti, Urbano, Delodder, Kaplan, & Oddo, 2010; Rundgren et al., 2010; Scozzafava, Hussain, Brindley, Jacka, & Gross, 2010; Wennervirta et al., 2009; Young, 2000; Zandbergen et al., 2006). Also,

in patients who developed EEG status epilepticus after cardiac arrest, those who initially showed BSP developed it earlier than those with previous continuous EEG (Rundgren et al., 2010). Additionally, unlike other patients with status epilepticus after cardiac arrest, those who also developed seizures and a 'malignant' pattern (BSP, nonreactive/flat background) were very unlikely to benefit from aggressive antiepileptic therapy to regain consciousness (Fugate et al., 2010; Rossetti, Oddo, Logroscino, & Kaplan, 2010; Rundgren et al., 2010; Thömke & Weilemann, 2010). For the prediction of poor neurologic outcome after cardiac arrest in the first 24-h period, a Burst Suppression Rate (BSR) >21.5% has 89% sensitivity, 62% specificity, a positive prediction value of 50% and a negative prediction value of 93%. The critical range of 20 to 25% of EEG BSR measured 24 to 96 h after admission to the ICU has the highest correlation to poor outcome (Theilen et al., 2000). Additionally, a review concluded that during therapeutic hypothermia or shortly thereafter, EEG showing unreactive/spontaneous BSP, together with absent N20 on somatosensory evoked potentials, is almost 100% predictive of irreversible coma (Oddo & Rossetti, 2011).

A prospective study compared the survival rate of 681 patients undergoing emergency EEGs (Borges et al., 2010). The EEGs were performed for several reasons including status epilepticus, hepatic encephalopathy and impaired consciousness. Patients with BSP had the lowest survival rate 1 month following EEG (25% vs. 50-75% for other EEGs). In these patients, the BSP occurred as a consequence of anesthetic administration during the treatment of status epilepticus, anoxia following cardiorespiratory arrest or other serious lesions of the CNS such as head-brain injury and intra-parenchymatous hemorrhage.

BSP-related syndromes

BSP is a well-known feature of some neonatal encephalopathies. The main neonatal encephalopathies showing this EEG pattern and their main characteristics are listed in table 5.

Asynchronous BSP appears in the pediatric Aicardi's syndrome and some early myoclonic encephalopathies. In these syndromes a partial or complete agenesis of the corpus callosum is frequent, which could explain the asynchrony of the BSP between the two hemispheres (Dobyns, 1989; Rossi, Daniele, Bastrenta, Mastrangelo, & Lista, 2009; Shah, Rajadhyaksha, Shah, & Wakde, 1992; Suzuki, Kure, Oota, Hino, & Fukuda, 2010; Yis, Kurul, & Dirik, 2009).

BSP and sleep

MacKay et al. (MacKay et al., 2010) suggested that episodes of BSP or near-burst suppression in the anesthetized patient might be the equivalent to the 'up-down' oscillations seen during some phases of natural sleep. If this is the case, these phenomena would share neuronal mechanisms. Interestingly, in terms of electrophysiological characteristics, some kind of relationship might be proposed between BSP and sleep; during BSP there are sharp waves, which resemble the vertex waves seen during sleep and have a distribution similar to that of spindles (San-Juan, Cole, & Chiappa, 2010). "Spindle-like" waveforms have been described in BSP as waxing and waning patterns of 13–20 Hz with a very pointed waveform similar to that of μ-rhythms (Huotari et al., 2004; Joutsen et al., 2009). The spindles associated with sleep, barbiturates and probably other kinds of anesthesia are generated in the thalamus and distributed to the neocortex through thalamo-cortical pathways (Feshchenko, Veselis, & Reinsel, 2004;

Table 5. Neonatal encephalopathies showing BSP.

Encephalopathy*	Main characteristics
Ohtahara syndrome (Ohtahara & Yamatogi, 2003, 2006; Williams, Gray, Poulton, Ramani, & Whitehouse, 1998)	An early infantile epileptic encephalopathy presenting mainly in the first 10 days of life. It is associated with brain atrophy and metabolic dysfunction. Infants develop intractable seizures, mainly tonic spasms and with age present developmental and cognitive problems. With age it evolves to West syndrome and later to Lennox-Gastaut syndrome. BSP has the same characteristics during both waking and sleeping states and generally disappears after 3-4 months of age
Early myoclonic encephalopathy (Lombroso, 1990; Ohtahara & Yamatogi, 2006; Rossi et al., 2009; Suzuki et al., 2010; Yis et al., 2009)	An early infantile epileptic encephalopathy presenting in the first month of life. Myoclonia and frequent partial motor seizure are the main seizures. Its principal known cause is nonketotic hyperglycemia, also known as glycine encephalopathy, an inborn metabolic disorder in which glycine, which acts as an inhibitory neurotransmitter in the brainstem and spinal cord but has an excitatory function in the brain cortex, accumulates in all body compartments. It may present a transitory phase of West syndrome BSP becomes more apparent during sleep than during waking state and may persist until late infancy after a transient change into hypsarrythmia.
Aicardi's syndrome (Dobyns, 1989; Shah et al., 1992)	A rare genetic syndrome that only affects girls. It is characterized by the complete or partial absence of the corpus callosum. Infants develop seizures and other neurologic disorders. Some girls may present with coloboma or microphthalmia. BSP is characteristically asynchronous between the two hemispheres

*BSP is also relatively common in other neonatal encephalopathies such as neonatal hypoxic encephalopathy, structural brain damage, cryptogenic encephalopathies and other metabolic disorders, which can cause seizures with BSP (Volpe, 2008).

Mackenzie, Pope, & Willoughby, 2004; San-Juan et al., 2010; Sonkajärvi et al., 2008; Steriade, Gloor, Llinás, Lopes de Silva, & Mesulam, 1990). The mechanisms behind the production of these shared EEG patterns are probably present in both BSP and sleep (San-Juan et al., 2010; Sonkajärvi et al., 2008). However, similarities known to date are very few and a real equivalence between BSP state and sleep stages, as that proposed by MacKay et al. (2010), is far from being demonstrated.

Even though BSP does not appear in normal sleep (Brown, Lydic, & Schiff, 2010), a burst-suppression-like pattern known as "trace alternant" phenomenon is present in some healthy newborns during drowsiness and all stages of sleep (Thordstein et al., 2004). As it can be seen in Figure 3, trace alternant pattern is considerably similar to BSP. This phenomenon possibly represents a state of optimization of brain energy in the absence of higher order functions during early development, as BSP is suggested to be a means of cell preservation (Ching et al., 2012).

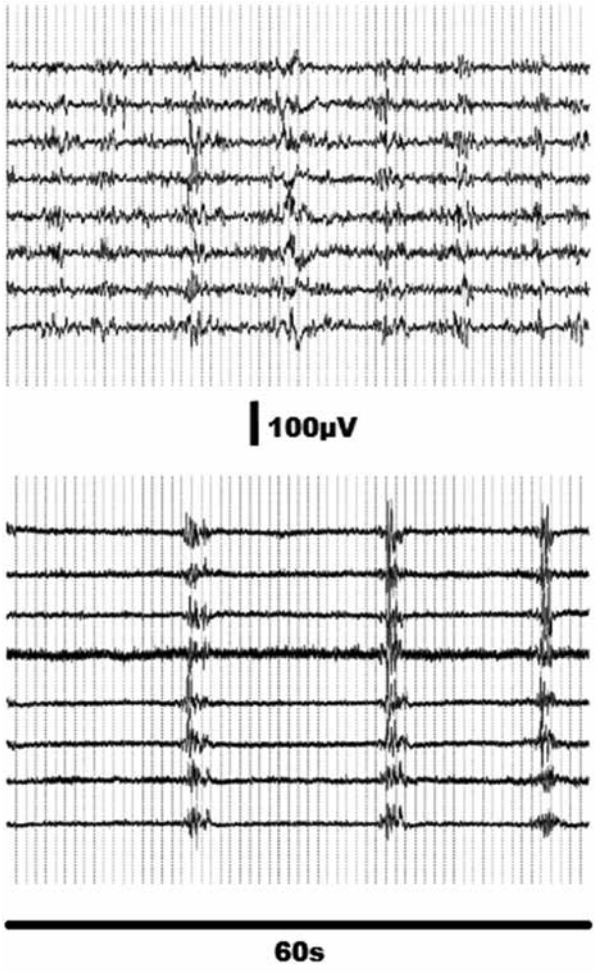

Figure 3. Above: trace alternant pattern in a healthy newborn. Below: BSP in a newborn who suffered from intrapartum asphyxia. (Figure from Thordstein M, Flisberg A, Löfgren N, Bågenholm R, Lindecrantz K, Wallin BG, et al. Spectral analysis of burst periods in EEG from healthy and post-asphyctic full-term neonates. Clinical Neurophysiology 2004;115(11):2461-6).

Neural origin of BSP

Although the neuronal mechanisms behind the onset and maintenance of BSP are not well known, evidence available might indicate that some neuronal circuits have a certain kind of activity during BSP and some theories can be suggested about the processes behind this brain state.

The variety of etiologies (De Rubeis & Young, 2001; Ferron et al., 2009; Kroeger & Amzica, 2007; Michenfelder & Milde, 1991; Ostermann et al., 2000; Pagni & Courjon, 1964; Weissenborn et al., 1991), the presence of slow/δ oscillations also observed during sleep and general anesthesia (Kroeger & Amzica, 2007), the homogeneous behavior of this pattern across the entire cortex (Hudetz & Imas, 2007; Steriade, Amzica, & Contreras, 1994; Swank, 1949) and other facts indicate that BS pattern represents a low-order dynamic mechanism that persists in the absence of higher-level mechanisms (Ching et al., 2012) and suggest common cellular mechanisms (Ferron et al., 2009).

There is evidence of spontaneous cerebral blood flow/blood-oxygen-level-dependent fluctuations within coherent neuronal networks under BSP anesthesia conditions (Vincent et al., 2007). Spontaneous hemodynamic signals fluctuate coherently within many resting-brain functional networks related to, for example, the motor, visual, auditory, thalamus, hippocampus, language, and default-mode systems (Biswal, Yetkin, Haughton, & Hyde, 1995; Cordes et al., 2000; Fair et al., 2008; Fox & Raichle, 2007; Greicius, Krasnow, Reiss, & Menon, 2003; Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002; He, Snyder, Zempel, Smyth, & Raichle, 2008; X. Liu, Zhu, Zhang, & Chen, 2011; Lowe, Mock, & Sorenson, 1998; Stein et al., 2000; Vincent et al., 2007). These hemodynamic fluctuations seem to originate mainly from underlying spontaneous high-voltage burst activity (X. Liu et al., 2011). The correlation between EEG bursts and hemodynamic fluctuations could be due to the synchronization of bursts across a large number of neurons (X. Liu et al., 2011), so activity within these neuronal networks might be the origin of EEG bursts.

Thalamo-cortical circuits were believed to be the primary generators of bursting in the anesthetized patient (Steriade, 2006; Steriade, McCormick, & Sejnowski, 1993) and some authors suggested that the burst firing mode depended on thalamic-hyperpolarization-activated excitatory currents (Robinson & Siegelbaum, 2003; Sleigh, Leslie, & Voss, 2010). However, undercut anesthetized neocortex can still generate BSP activity (Swank, 1949; Topolnik, Steriade, & Timofeev, 2003) and BSP activity has been demonstrated in the isolated cortex of men undergoing prefrontal lobotomy (Henry & Scoville, 1952) and in isolated neocortical brain slice preparations without subcortical input (Lukatch & MacIver, 1996). Also, a computational model demonstrated how the features of BSP may arise using a purely cortical network (Ching et al., 2012). This

evidence supports the idea that thalamo-cortical circuits do not have to be intact for the production of BSP and that there is an intrinsic mechanism in the cortex and in networks showing activity during bursts that would lead to BSP activity. However, given the high synchronization of BSP across the entire brain (Akrawi et al., 1996; Cissé, Wang, Inoue, & Kido, 2010; Hudetz & Imas, 2007; MacIver, Mandema, Stanski, & Bland, 1996; Silva et al., 2010; Steriade et al., 1994; Swank, 1949) that is lost when circuits are disconnected (Henry & Scoville, 1952; Lazar, Milrod, Solomon, & Labar, 1999; Stern, 2005); the intrinsic mechanisms of BSP must regulate each other within the intact brain.

During deep anesthesia without BSP, α rhythm characterizes the spectrogram (Ching, Cimenser, Purdon, Brown, & Kopell, 2010; Cimenser et al., 2011; Purdon et al., 2009). During bursts in BSP EEG, this α rhythm persists (Hudetz & Imas, 2007; Purdon et al., 2009), indicating that the mechanisms for α rhythm genesis survive the onset of BSP (Ching et al., 2012). The propofol-induced α rhythm involves potentiation of GABA inhibitory currents in thalamo-cortical loops (Brown, Purdon, & Van Dort, 2011; Ching et al., 2010). Thus, this could be one of the multiple neuronal mechanisms present during burst of BSP. However, as was discussed before, thalamo-cortical circuits do not have to be intact for generating BSP in cortex (Swank, 1949; Topolnik et al., 2003), so α activity, although present in an intact brain during BSP, is not the essential mechanism behind this brain state.

It has been shown that during BSP there is a hyperexcitable state of the cortex in which low intensity stimuli are able to elicit EEG burst activity, which would not be overt under normal conditions (Kroeger & Amzica, 2007). The fact that during isoflurane-induced BSP extracellular chloride is increased, probably because of the inactivity of GABA receptors, leads to suggest that hyperexcitability is the result of abolished inhibition rather than increased excitation (Ferron et al., 2009). When BSP is achieved, overt inhibitory potentials following excitatory post-synaptic potentials in cortical neurons are abolished. Diminished inhibition during BSP is not caused by GABA receptor blockage because iontophoretically applied GABA has demonstrated receptor availability (Ferron et al., 2009). Isoflurane has been shown to stimulate glutamate uptake by the glial glutamate transporter (GLT1/EAAT2) (Larsen, Hegstad, Berg-Johnsen, & Langmoen, 1997; Zuo, 2001). The restoration of inhibitory responses to thalamic stimulation in cortical neurons after application of the selective blocker of glial glutamate transporters, dihydrokainate, leads to suggest that the diminished inhibition during BSP is mainly due to isoflurane-induced reduction of glutamate availability within cortical networks and the consequent reduction of excitatory neuronal inputs to inhibitory interneurons (Ferron et al., 2009). Thus, this diminished inhibition appears to be the result of a generalized reduction in excitation that leads to a reduced activation of inhibitory interneurons (Ferron et al., 2009). Diminished inhibition could also be achieved through isoflurane-induced reduction in synaptic release of glutamate (Maclver, Mikulec, Amagasu, & Monroe, 1996; Westphalen & Hemmings, 2003; Wu, Sun, Evers, Crowder, & Wu, 2004), and/or blockage of postsynaptic AMPA receptors of glutamate (Dildy-Mayfield, Eger, & Harris, 1996). The fact that during this state of diminished inhibition low intensity stimuli can elicit bursts that would not be overt in other conditions (Kroeger & Amzica, 2007) has led some authors to suggest that the source of bursts may be ascending inputs since external stimuli have been shown to evoke bursts of cortical activity (K. Hartikainen & Rorarius, 1999; K. M. Hartikainen, Rorarius, Peräkylä, Laippala, & Jäntti, 1995; Hudetz & Imas, 2007; Rojas, Navas, Greene, & Rector, 2008; Rojas, Navas, & Rector, 2006; Yli-Hankala, Jäntti, Pyykkö, & Lindgren, 1993), and bursts at cortical and subcortical sites may be highly synchronized (Akrawi et al., 1996; MacIver et al., 1996). However, bursts could also be originated from intrinsic neuronal networks mechanisms as shown in previous paragraphs (Swank, 1949; Topolnik et al., 2003). Thus, although it is known that ascending inputs to brain may elicit bursts, this would not be the only factor responsible for the production of bursts during BSP. Actually, the most reasonable explanation would be that intrinsic mechanisms of circuits able to generate BSP are responsible for the production of bursts, but ascending input to brain and reciprocal interactions between these circuits play a role in modulating their activity. The ascending inputs would play an activator role, whereas reciprocal interactions of these circuits would regulate their synchronization in a way that is so far unknown.

One important theory to explain the intrinsic mechanisms responsible for the production of BSP came from the model developed by S. Ching et al. (2012). They suggested that the link between reduced cerebral metabolism and BSP could be the ATP-gated potassium channel (KATP) or channels that behave similarly because KATP is thought to provide neuronal protection during hypoxic-ischemic events (Murdoch & Hall, 1990; Wang et al., 2011). The neurophysiological metabolic model for BSP developed by them also suggests that the principal features of BSP EEG represent a basal neurometabolic regime that ensures basic cell function during stages of lowered metabolism (Ching et al., 2012). In this model, the KATP channel modulates neuronal firing as a function of ATP production. The rate of ATP production is, in turn, directly modulated by the cerebral metabolic rate of oxygen consumption. Activation of this channel serves to stabilize cell membranes, leading to seconds-long periods of alternating suppression and activity. In this model, ATP concentration decreased by approximately 25% as bursts occurred, which caused an increase in the conductance of KATP (gKATP). The opening of KATP led to hyperpolarization and thus to the suppression phase. During suppression, ATP concentration slowly

recovered until gKATP was reduced to a point where spikes could occur again. Thus, this model could argue that the progressive increase of BSR that is associated with deeper levels of inactivation may be due to a reduction in metabolism. The spatial synchronization of this pattern across cortical and subcortical structures could also be the broad manifestation of such metabolic changes. Finally, the recovery of α-rhythms within bursts could be the manifestation of the recovery of the network basal dynamics during a temporal recovery of energy. This mechanism implies that BSP is a means for cell preservation, preserving maximum energy for basic cell functions (Ching et al., 2012). This model would also explain the reported refractory time necessary for the production of a new burst following external micro-stimulation (Kroeger & Amzica, 2007).

Extracellular calcium correlates with the switches between bursts and isoelectricity periods of BSP EEG (Ferron et al., 2009; Kroeger & Amzica, 2007). Because extracellular calcium depletion prohibits synaptic transmission, it is suggested to lead to suppression periods that then alternate with activity periods (Amzica, 2009). This view could be a companion to the mechanisms suggested in the afore mentioned model because ATP reductions and opening of KATP channels may contribute, respectively, to the depletion and restoration of extracellular calcium levels (Ching et al., 2012).

Electrical activity of CNS regions during BSP

In the next subsections we describe electrical activity of different CNS regions and coherent activity between them during BSP. However, it is worth mentioning that the neurobiological meaning and practical applications of most of these reported electrical activities are almost totally unknown:

1 - Cortex activity: The BSP activity is widely synchronized across the entire neocortex (Hudetz & Imas, 2007; Steriade et al., 1994; Swank, 1949), but also across cortical and subcortical structures such as hippocampus and thalamus (Akrawi et al., 1996; Cissé et al., 2010; MacIver et al., 1996; Silva et al., 2010). However, the strength of the bursts may not be uniform over these brain regions (Hudetz & Imas, 2007). Throughout induction and recovery from anesthesia, including BSP state, a slow cortical potential (<0.5 Hz) oscillation over the somatomotor cortex remains unchanged (Breshears et al., 2010).

2 - Thalamic activity: A study evaluated deep coherence patterns at the thalamic level in human beings using electrodes implanted with spacing of 1.5 mm (Silfverhuth et al., 2010) . Continuous comparisons between electrodes were made from induction of propofol anesthesia until BSP occurred. A high coherence in the α band from the thalamus was found at all times, even during BSP. This occurred in both bilateral and ipsilateral comparisons. Coherence decreased with spatial relationship in all other frequencies except in α band. Authors of this study claimed that persistent α coherence in the thalamus emphasizes the fundamental nature of alpha oscillations.

3 - Thalamo-cortical activity: When recording local field potentials in somatosensory cortex and thalamic regions during anesthesia, a high coherence activity in δ, θ, α, β and γ frequency bands is detected, even during BSP (Silva et al., 2010). In the same way, BSP appears simultaneously in these two areas and is highly synchronized between them (Silva et al., 2010). Although during isoelectric periods of anesthesia-induced BSP sensory response of cortical cells is lower than that of thalamic cells (Detsch, Kochs, Siemers, Bromm, & Vahle-Hinz, 2002; Vahle-Hinz, Detsch, Siemers, & Kochs, 2007), concordance of rhythms and BSP between these structures could represent the persistence of a "permanent cortico-thalamic dialogue" during BSP. However, the power of BSP may vary between these two regions at different BSRs. A higher percentage of cortical cells (95%) than thalamic cells (60-70%) reaches a firing pattern coherent to EEG BSP early (Steriade et al., 1994), so thalamic cells discharge even during silent EEG periods at lower BSRs. Only when isoelectric BSP periods are longer than 30 sec all thalamic cells discharge and have silence periods coherent to bursts and isoelectricity EEG, respectively.

4 - Hippocampal-cortical activity: There is coupling of θ–γ oscillations in the neocortex that is maintained even during BSP (Breshears et al., 2010; Canolty et al., 2006). Because θ rhythms are related to hippocampal processing (Axmacher et al., 2010; Buzsáki, 2002), θ–γ coupling might represent preserved hippocampal-cortical interactions during BSP (Breshears et al., 2010). Additionally, a low amplitude fluctuation of 4–14 Hz (mainly θ and α) has been reported during BSP periods of anesthesia with localization in the hippocampus and reflection in the cortex (Cissé et al., 2010). The power of this activity increases in the hippocampus and anterior parahippocampal gyrus with increasing depth of anesthesia. There is also a reduced chaos within the rhinal cortex as anesthesia deepens (Fell, Widman, Rehberg, Elger, & Fernández, 2005).

5 - Spinal cord activity: During BSP anesthesia, even though there is low excitability of alpha motor neurons (Rampil & King, 1996), it is still possible to excite them because BSP anesthesia does not totally abolish the motor response (Haberham et al., 1999; Haga et al., 2002).

Factors leading to differences in the BSP

1 - Variations in BSR: During a study using propofol-remifentanil anesthesia in 1494 patients, factors associated with the BSR were determined (Besch et al., 2011). A higher BSR was associated with advance age, history of coronary artery disease and male gender. Age has been shown elsewhere to correlate with the presence of BSP and with a higher BSR in the

EEG of anesthetized subjects (A. Schultz et al., 2004; B. Schultz, Schultz, Grouven, Zander, & Pichlmayr, 1995; Sleigh et al., 2010). Additionally total EEG power when BSP occurs gets significantly smaller in patients aged 70 years and older, mostly due to a distinctly smaller absolute power within the δ frequency band (San-Juan et al., 2010). Lower temperature levels also correlate with higher values of BSR (Otto, Höffler, Cebotari, & Tudorache, 2011) and with an earlier appearance of BSP as anesthetic concentration gradually increases (Woodcock et al., 1987). However, although deep hypothermia may result in high BSR, EEG is not significantly affected at a body temperature greater than 33°C (Michenfelder & Milde, 1991; Stecker et al., 2001a). Similar to the progression observed during the emergence from general anesthesia, as hypothermia is gradually corrected the BSR decreases until a continuous EEG is recovered (Levy et al., 2003; Stecker, 2007).

The higher prevalence of BSP and levels of BSR in the elderly might be due to alterations in anesthetic pharmacokinetic and pharmacodynamic responses in elderly patients (Minto et al., 1997; Schnider et al., 1999) or to a reduced skull conductivity induced by ageing (Wendel, Väisänen, Seemann, Hyttinen, & Malmivuo, 2010). Hypovolemia or decreases in cardiac output could favor the increase of BSR in patients with history of coronary artery disease because they have been shown to modify the pharmacokinetics and pharmacodynamics of anesthetics (Takizawa, Takizawa, Hiraoka, Saito, & Goto, 2006). The lower prevalence of BSR in women might be explained by sex-related differences in the pharmacodynamic effect of anesthetic agents (Gan et al., 1999; Hoymork & Raeder, 2005). Lastly, the depressant effect of hypothermia on EEG is suggested to be reached through the direct reduction of the brain's metabolic rate and the reduction of the minimal alveolar concentration for inhaled anesthetics (Eger, Saidman, & Brandstater, 1965; Marion et al., 1997; Michenfelder & Milde, 1991; Otto et al., 2011).

Other factors that have been associated with higher levels of BSR are manual administration of propofol-remifentanil anesthesia when compared to automatic closed-loop delivery (N. Liu et al., 2011) and a slower propofol administration (Jang et al., 2009).

2 - Asynchrony of BSP: Some studies have suggested that asynchronous BSP across the scalp can arise in the case of large-scale cortical deafferentation (Henry & Scoville, 1952; Lazar et al., 1999). Unilateral brain dysfunction, for instance, after unilateral stroke (Stern, 2005), and lesions in the corpus callosum result in an abnormal synchronization (asymmetry) of the BSP between the two hemispheres (Hukin et al., 2005; Lambrakis, Lancman, & Romano, 1999; Lazar et al., 1999; Savard & Huot, 2008; Shah et al., 1992; Stern, 2005; Swank, 1949). In such settings, differences in regional blood supply and auto-regulation may prevent the uniformity typically associated with burst suppression (Ching et al., 2012).

Stimulus-related effects

1 - Somatosensory-evoked potentials (SEPs): SEPs have been recorded during isoflurane-, sevoflurane- and propofol-induced BSP (Joutsen et al., 2009; Jäntti et al., 1998; MacDonald, Al Zayed, & Stigsby, 2005; Porkkala, Kaukinen, Häkkinen, & Jäntti, 1997; Rytky et al., 1999). Due to the low levels of noise in the SEPs frequency bands during suppression phases of BSP, and because of the enhancement of the first cortical components of the SEPs, SEPs are more easily identified in this stage than during the rest of BSP (Joutsen et al., 2009; Jäntti et al., 1998; Rytky et al., 1999). The major source of BSP noise in SEP recordings is the mixed frequency activity of the slow waves of bursts that occur during propofol anesthesia. Spindles during burst suppression also have frequency components that increase noise levels, but these are less important because the number of spindles is fewer. Thus, averaging the SEPs selectively during the suppression phases can yield reliable SEPs in one-fifth to one-tenth of the time compared to sampling during either burst phases or continuous EEGs immediately before the onset of BSP (Joutsen et al., 2009).

2 - Evoked bursts during BSP: There is evidence of late evoked burst responses synchronized to external stimuli (visual, auditory, and somatosensory) during BSP induced by anesthetics (K. Hartikainen & Rorarius, 1999; K. M. Hartikainen et al., 1995; Hudetz & Imas, 2007; Rojas et al., 2008; Rojas et al., 2006; Yli-Hankala et al., 1993). In a study using rats anesthetized with isoflurane at a constant dose clapping was the stimulus that provoked the highest decrease in the BSR, followed by a familiar voice, an unfamiliar voice and finally by a toe pinch (Rojas et al., 2008). Additionally, a study described differences in waveform and latency of the bursts specific to the modality of stimulation (K. M. Hartikainen et al., 1995). Thus, there are differential sensory responses in cortex during BSP-anesthesia, which might represent unconscious sensory processing. After each burst of BSP induced by anesthesia, there is a period in which no more bursts can be evoked through external micro stimulation. Such diminished cortical excitability converts to enhanced excitability as ATP gradually recovers (Kroeger & Amzica, 2007).

3 - Noxious response: In anesthetized adult patients incision associates with a significant loss of BSP (decrease in BSR) (MacKay et al., 2010; Sleigh et al., 2010), which is one of the changes associated with a more "continuous" EEG after incision. This decrease in BSR is independent of both the anesthetic drug used and the pre-incision BIS, but seems to be greater in patients with higher levels of BSR prior to noxious stimulation (MacKay et al., 2010; Sleigh et al., 2010). Incision activates various excitatory neuromodulators (amines, acetyl choline, orexin, and glutamate). Such activation would lead to a certain degree of depolarization of the thalamo-cortical system (Alkire, 2008; Alkire, Hudetz, & Tononi, 2008; Antognini & Carstens, 2002). It was proposed that incision would cause the observed loss

of burst suppression through thalamic depolarization (Sleigh et al., 2010).

Conclusions

BSP is present in many pathologic and physiologic conditions. It is mainly known by its appearance in patients under deep anesthesia conditions, but BSP is also usual in conditions that globally affect brain such as hypothermia and diffuse brain damage from different etiologies. A very similar phenomenon known as trace alternant is also seen in healthy newborns during drowsiness and during any stage of sleep.

BSP EEG is not a discrete state, but occurs on a continuum guided by changes of the underlying biophysical processes. These biophysical processes are those implicated on the degree of brain metabolism because BSP appears to be a state of optimization of brain energy under conditions of limited energy availability or use. Factors influencing these processes include drugs, toxins, brain´s oxygen requirements, oxygen availability for brain, temperature, sensitive input to brain and maybe intrinsic brain processing.

Bursts are probably the consequence of intrinsic mechanisms of cortex and coherent neuronal networks, but their production is regulated by the factors mentioned in the previous paragraph that lead to a certain degree of activation or inactivation of these intrinsic mechanisms. For instance, sensitive input to brain would play an activator role, whereas a decrease in temperature would play an inhibitory role. Additionally, communication between areas able to intrinsically generate a BSP would regulate and synchronize bursts across them in a way that is not understood so far. The isoelectric periods could be the manifestation of depletion of ATP that leads to hyperpolarization of cells as ATP is gradually recovered to elicit a new burst.

Finally, it is worth mentioning that the current knowledge about BSP is extremely limited and dispersed. After an exhaustive review of the literature, the information we found was considerably ambiguous and at times even contradictory. Future research is needed to elucidate many aspects, mainly those surrounding the neuronal mechanisms behind the BSP brain state.

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