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INVITED REVIEW

Breath-holding as model for the evaluation of EEG signal during respiratory distress

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Abstract

Purpose Research describes the existence of a relationship between cortical activity and the regulation of bulbar respiratory centers through the evaluation of the electroencephalographic (EEG) signal during respiratory challenges. For example, we found evidences of a reduction in the frequency of the EEG (alpha band) in both divers and non-divers during apnea tests. For instance, this reduction was more prominent in divers due to the greater physiological disturbance resulting from longer apnea time. However, little is known about EEG adaptations during tests of maximal apnea, a test that voluntarily stops breathing and induces dyspnea.

Results Through this mini-review, we verified that a protocol of successive apneas triggers a significant increase in the maximum apnea time and we hypothesized that successive maximal apnea test could be a powerful model for the study of cortical activity during respiratory distress.

Conclusion Dyspnea is a multifactorial symptom and we believe that performing a successive maximal apnea protocol is possible to understand some factors that determine the sensation of dyspnea through the EEG signal, especially in people not trained in apnea.

Keywords Apnea · Cerebral cortex · Diving · Dyspnea · Electroencephalography · Immersion

Introduction

The electroencephalographic signal (EEG) is a parameter obtained through the assessment of cortical brain activity (Muller-Putz 2020) which consists of brain electrical impulses, enabling its classification according to amplitude, frequency, and wave latency (Lee et al. 2015; Dimitriadis et al. 2018). Research has described the existence of a close relationship between cortex activity and the regulation of respiratory centers (Thayer and Lane 2009), and the possibility of evaluating the relationship between respiratory and cortical function through electroencephalography (Macefield and Gandevia 1991; Tort et al. 2018). Such interaction originates from the central autonomic network, an interconnected self-regulation system responsible for controlling behavioral, neurochemical, and visceromotor responses (Benarroch 1993), whose structures include the insular cortex, amygdaloid nucleus, hypothalamus, and solitary tract nucleus (NTS) in the medulla that connects with the spinal cord and afferent (sensory) and efferent (motor) neurons (Napadow et al. 2008).

Several assessment protocols have been used to detect changes in cortical activity through respiratory "challenges", such as resistance inhalations and repeated voluntary nasal sniffs (Hudson et al. 2018). The voluntary apnea test is another example of a respiratory maneuver that consists of consciously suspending breathing (Elia et al. 2021). Its main performance parameters are the moment that the feeling of "air hunger" starts or more conveniently defined as the physiological breaking point (Agostoni 1963; Lin et al. 1974) and the maximum duration of the apnea. These outcomes may change under different conditions, for example:

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depending on the respiratory technique used before apnea, such as glosso-pharyngeal breathing (Lindholm and Nyrén 2005; Lemaître et al. 2010; Schipke et al. 2015), the level of partial or total lung insufflation at apnea start (Findley et al. 1983; Whitelaw et al. 1987; Flume et al. 1996; Andersson and Schagatay 1998), beta-1 adrenergic blockade (Hoiland et al. 2017), performing the technique in a dry environment or with one's face submerged in water or during diving (Sterba and Lundgren 1988; Schagatay and Andersson 1998; Schagatay et al. 1999; Lemaître et al. 2007; Ratmanova et al. 2016; Elia et al. 2021), in individuals trained in apnea (Schagatay et al. 2000; Diniz et al. 2014), with different abilities to withstand the "urge to breathe" during apnea (Ferretti 2001; Menicucci et al. 2014), who experience psychological symptoms such as fear and anxiety (Rassovsky et al. 2006; Freire and Nardi 2012), with different intensities of dyspnea (Nishino 2011), or those who have pre-existing respiratory diseases (Nannini et al. 2007; Inoue et al. 2009; Viecili et al. 2011, 2012).

Based on evidence that successive apneas protocol increases the maximum apnea time (Heath and Irwin 1968; Bartlett 1977; Schagatay et al. 1999) and that the longer the maximum apnea time during breath-hold diving more significant are the reductions in the electroencephalographic signal (Steinberg et al. 2017), the hypothesis of this mini-review is that a successive apnea protocol is a promising model that can be used to take the electroencephalographic signal to lower frequencies and to understand the determinants of "air hunger" and dyspnea through comparison of the activity of the cerebral cortex between low and high physical fitness people or with comorbidities. This hypothesis study intends to suggest possibilities for future studies analyze mechanisms of dyspnea through the evaluation adaptations of the EEG signal during respiratory distress through of successive apneas protocol.

Connection between the cerebral cortex and the respiratory system

The central autonomic network is made up of billions of neurons that individually establish thousands of connections with different regions of the brain responsible for various vital functions. Among them is the NTS, a complex of nuclei capable of regulating various cognitive, neuroendocrine, and autonomic functions (Priovoulos et al. 2019). It is framed as a visceral sensorimotor nucleus located in the caudal and dorsomedial part of the medulla that receives, processes, and coordinates both respiratory and cardiovascular inputs through its connection with nerves and the spinal cord (Zoccal et al. 2014). It plays a key role in integrating and coupling the both respiratory and cardiovascular function through the neural network that it coordinates. This region of the central nervous system receives sensory informations via afferent pathways by means of the Glossopharyngeal and Vagus nerves, which comes from baroreceptor and chemoreceptors situated in the aortic and carotid bodies, which are responsible for capturing changes in O_2 and CO_2 pressure, in addition to systemic blood pressure (Guyenet et al. 2010). The Vagus nerve is also responsible for transmitting information from pulmonary and juxtacapillary stretch receptors that also influence respiratory control (Marek et al. 2008). Currently, several authors recognize the input of proprioceptive and chemical sensory information coming from the respiratory muscles (especially the diaphragm) through the phrenic nerve (Bordoni and Zanier 2013) and proprioceptive information coming from the joints and locomotor skeletal muscles (Parkes 2006). In addition to peripheral stimuli, the NTS is directly influenced by CO_2 that move across the blood–brain barrier and stimulates the central H^+ chemoreceptor and the respiratory centers of the bulb and triggers important respiratory responses (Nattie and Li 2012; Guyenet 2014). Sensory responses probably also reach higher cortical centers, influencing subjective respiratory sensation and voluntary respiratory command. Based on input from afferent (involuntary) and cortical (voluntary) information, the NTS is responsible for producing a respiratory motor response (central respiratory rhythm) that regulates the contraction of the respiratory muscles. Motor command starts at the bulbar inspiratory center and is prolonged when stimulated by the apneustic center or interrupted by the pneumotaxic center and reaches the respiratory muscles via the phrenic nerve.

The voluntary interruption of breathing triggers chemical processes that can result in the sensitization of peripheral CO_2 (hypercapnia), O_2 (hypoxemia), and central H^+ (acidosis) chemoreceptors, and their afferent actions are essential for the homeostasis of blood gases and for stimulating ventilation and are considered crucial in determining the apnea breaking points (Lin 1982; Foster and Sheel 2005; Lindholm and Lundgren 2009; Guyenet et al. 2013; Fitz-Clarke 2018; Taboni et al. 2020). Non-chemical (mechanical) factors such as the degree of stretching of the lung parenchyma determined by the volume of air in the lungs and sensory feedback from the respiratory muscles, especially the diaphragm, also trigger ventilatory responses and the breaking point, namely involuntary interruption apnea (Parkes 2006; Nishino 2009). Agostoni's seminal study (1963) and subsequently other studies (Lin et al. 1974; Palada et al. 2008; Cross et al. 2013) confirmed the onset of diaphragmatic contractions to precede the volitional breaking point. Additionally, it was suggested that the onset of diaphragmatic contractions give origin to the final phase of the cardiovascular response to apnea, in which blood pressure increases and heart rate (HR) tends to decrease (Perini et al. 2008; 2010). Despite the importance of physiological factors (Ferretti

et al. 1991; Delapille et al. 2001), the psychological factor is another parameter that can influence apnea performance. Although it is often overlooked, respiratory and cardiovascular signals that reach the brain are transmitted via the parabrachial subnuclei to different regions of the brain via the central autonomic network and converted into basic emotions related to respiratory distress and the urge to breathe. These sensations and feelings can limit apnea performance by participating in the control of breathing through the central autonomic network and supports the concept of a "wakefulness drive" that can have a profound impact on respiratory and cardiovascular control (Thornton et al. 2001; Martelli et al. 2013). In any case, from an integrative perspective, the time to the physiological breaking point should be directly proportional to the size of body oxygen stores (Fagoni et al. 2015; Taboni et al. 2018) and inversely proportional to the rate of body oxygen consumption (Sivieri et al. 2015), since the breath-hold duration was prolonged in hyperoxia (Klocke and Rahn 1959) and was shortened during hypoxia (Rahn et al. 1953). These adaptations are interpreted as an O_2-conserving mechanism (Ferretti 2001).

Insufficient O_2 can affect brain activity (Pearce 2018). It can result in cognitive deficits, such as attention deficit, mental confusion, memory loss, and syncope, and can cause psychomotor performance dysfunction such as hypomobility, weakness, loss of balance (Ando et al. 2020) and, in severe cases, seizures, coma, and brain death (Moral et al. 2019). Hypercapnia triggered by the ineffective pulmonary elimination of CO_2 can lead to changes in brain activity, in addition to causing respiratory acidosis and functional impairments, such as a feeling of suffocation, dizziness, syncope, anxiety attacks, and headache (Romano et al. 2016). In such cases, electroencephalography has been employed to assess the severity of blood gas disturbances in patients hospitalized for acute respiratory failure (Papadelis et al. 2017). This is an example of clinical application of EEG assessment during respiratory disorders.

Respiratory maneuver and cortical responses assessed by EEG

Bulbar respiratory control is responsible for managing and coordinating respiratory functions through its direct connection with the spinal cord, cranial nerves, and its interaction with the central nervous system. However, due to its anatomical location within the brainstem, its electroencephalographic evaluation is not feasible. Thus, for a long time, the use of the EEG for the study of phenomena associated with breathing was redundant. However, research has demonstrated the possibility of evaluating respiratory function through electroencephalography by means of its connection with the cerebral cortex (Macefield and Gandevia 1991).

Several studies have transcribed reports of the capture of bioelectrical signals from electroencephalography during respiratory maneuvers. Macefield and Gandevia (1991) are pioneers in demonstrating that premotor potentials precede inspiration or expiration in rapid breaths or voluntary exhalations, that is, changes present in the EEG can be perceived through the activation of premotor potentials originating from simple tasks, such as speaking or conscious respiratory disturbances. During speech, we involuntarily perform an automatic control of breathing, as this occurs during the process of expiration and controlled inhibition of inspiration. Before speaking, unconscious pre-phonatory inspirations occur that precede the pronunciation, intonation, and rhythm of speech. In this act, breath control activities related to speech occur, modeling pre-phonatory breaths originating in the cortical premotor areas, which can be evidenced on the electroencephalogram (Tremoureux et al. 2014).

As with phonation, other respiratory maneuvers can also produce changes in electroencephalographic signals, in addition to being a viable way to reduce artifacts during EEG collection. The practice of breathing techniques, such as diaphragmatic breathing, promotes the reduction of physiological responses linked to stress (Ma et al. 2017). For example, when taking a deep, slow inspiration, there is a synchronization of brain oscillations in the limbic network through the olfactory cortex. Stress and anxiety, on the other hand, cause respiratory disorders that result in short and rapid inspirations, thus causing a low level of cellular oxygenation due to reduced movement of the diaphragm muscles (Menicucci et al. 2014). Nasal breathing is closely related to the limbic system which is the area of the brain responsible for regulating emotions. The activity of chemoreceptors in detecting aromas during inspiration triggers impulses to the brain region of the olfactory cortex, where these signals are processed and associated with our memories and emotions (Laurent et al. 2001; Martin and Ravel 2014). Evidence demonstrated that cortical activity increased during nasal inspiration and dissipated when breathing was diverted from nose to mouth (Zelano et al. 2016). In this sense, breathing does not seem to serve only to supply oxygen to the body; it can also organize neuronal population activity across brain regions to orchestrate complex behaviors (Kleinfeld et al. 2014). This suggests a pathway by which nasal breathing could even shape rhythmic electrical activity in downstream limbic areas, with corresponding effects on cognitive functions (Zelano et al. 2016).

Apnea is another type of respiratory maneuver that provides interesting physiological and behavioral challenges for study with EEG. During a maximal apnea test, sensory impulses are produced by chemical factors such as increased arterial CO_2 ($PaCO_2$) levels. Hypoxaemia (reduced PaO_2) can also be seen in longer duration apnea tests. Factors of non-chemical (mechanical) origin are also observed from

lung tissue stretching and proprioceptive receptors of the respiratory muscles, especially the diaphragm (Delapille et al. 2001). Based on empirical definition, apnea has two phases: the first is called the easy phase and is characterized by less respiratory need, followed by the struggle phase which is characterized by respiratory distress and increasing electromyographic activity of the diaphragm and $PaCO_2$. Based on both respiratory and cardiovascular perspective, apnea can be divided into three phases: phase I, HR reduction and blood pressure increase; phase II, maintenance of HR and blood pressure values; phase III, progressive reduction in HR and arterial oxygen saturation and blood pressure increase until breaking point (Perini et al. 2008). Subjects with high maximal breath-holding time present all three phases; however, subjects with reduced performance present only phases I and II. While the duration of the easy phase seems to be influenced more by $PaCO_2$, the duration of the struggle phase is influenced by sensory stimuli produced by the respiratory muscles that maintain a tonic contraction, which is almost isometric, and is necessary to voluntarily maintain apnea (Nishino et al. 1996). Individuals not trained in apnea and/or diving have reduced maximum apnea time and both easy and struggle phases, while trained individuals have higher values. It is likely that the struggle phase is related to the III phase, in this sense, while subjects with lower performance end the apnea at the beginning of the III phase, subjects with higher performance endure the III phase for longer. The "urge to breathe" (distress) or "air hunger" during the struggle phase requires emotional endurance, motivation, and cognitive control to withstand discomfort. Apnea is a voluntary control event, and as time passes, sensory afferent signals increase the involuntary breathing stimulation until the breaking point, when the involuntary control interrupts the voluntary apnea stimulus. The prefrontal cortex is an area responsible for, among other functions, cognitive control (Miller and Cohen 2001), the mechanism of action and inhibition of cognitive response (Ridderinkhof et al. 2004), decision-making, performance monitoring, and learning, and, it seems, the voluntary control of apnea (Steinberg et al. 2017).

In this context, Ratmanova et al. (2016) raised the hypothesis that brain tissue hypoxia caused by voluntary apnea out of water could generate changes in the EEG and consequently in brain performance and attention span, especially in breath-hold divers. Despite the chronic changes observed in the EEG before the apnea test (professional divers showed a reduction in the alpha frequency approaching the theta band and an atypical spatial pattern of alpha amplitude when compared to non-divers), a few changes were observed in the EEG and in performance during apnea. The Direct Current potential (DC potential) suffered a small reduction from apnea but was stable until the end of the test in both divers and non-divers, with no significant differences between the groups. The total EEG spectrum amplitude during apnea did not differ from the pre-apnea situation nor between the groups. Contrary to the authors' expectations, attention deficit after breath-holding was not verified; on the contrary, the attention tests showed an increase, but with no difference between the groups regardless of the maximum apnea time (3 min for non-divers and 4.5 min for professional divers). Although apnea causes changes in the blood pressures of CO_2 and O_2, the results of this study refuted the hypothesis that hypoxia induces reduced brain activity, due to acute adaptations of the diving reflex aimed at centralizing blood circulation and reducing peripheral aerobic metabolism.

In another study, oscillations and asymmetries in the amplitude of the alpha band were verified during an out-of-water apnea test when comparing professional divers with non-divers (Steinberg et al. 2017). Initially, the authors found an increase in alpha amplitude in professional divers in the first two minutes of apnea in the central and parietal regions of the brain and a reduction in the non-diver group. After 2 min, the group of professional divers showed a significant decrease in the amplitude of alpha waves until the end of the apnea (four minutes of duration). This reduction was greater than that seen in the group of non-professionals (apnea lasting 2 min). The increase in alpha amplitude in the initial minutes in the group of professional divers was attributed to the ventilatory maneuvers and concentration techniques performed before the apnea test, leading to the conclusion that these pre-apnea techniques possibly contributed to a delay in the drop in alpha amplitude. The physiological adaptations provided by a longer apnea time produced a significant reduction in the frequency of alpha waves when compared to the pre-apnea situation only in the group of professional divers. Professional divers also showed an alpha-lateralized pattern (greater frontal activity on the left than on the right), possibly related to the psychophysiological process triggered by apnea (air hunger, resistance, motivation, emotional regulation, and cognitive control). In general, the reduction in the frequency of alpha waves is related to the reduction in cognitive performance, as it is associated with information processing speed and memory (Klimesch 2009). The effect of apnea on the reduction of the EEG frequency (alpha waves) seems to be an adaptive response to a lower cognitive need and an increase in attention for the person who is performing a certain task during apnea (Sinha et al. 2020).

Later, the same group published a study with the objective of verifying whether cognitive and psychological responses could be affected by the reduction in the frequency of the alpha band during out-of-water apnea. The performance of trained apnea divers was assessed using chess and visual activities during a pre-determined 4 min apnea period (Steinberg and Doppelmayr 2019). No significant changes were found in the responses of neurocognitive markers VEP and P300. The authors concluded that the short air retention time previously determined in 4 min was not sufficient to

produce a reduction in brain activity. Despite the significant reduction in the alpha band frequency seen earlier during a 4 min apnea test (Steinberg et al. 2017), this study failed to find changes in cognitive and psychological performance for the same period. These results were similar to the study carried out by Ratmanova et al. (2016), and according to the authors, a longer apnea time may be necessary to produce greater hypoxaemia and detect such changes.

Elite apnea divers can hold their breath for up to 11 min and thus produce hypoxaemia (Arce-Álvarez et al. 2021; Elia et al. 2021). The afferent stimuli triggered by hypercapnia and by proprioceptors of the respiratory muscles and lung tissue are delayed in these divers due to the adaptations provided by apnea training, allowing for longer duration apnea and, consequently, greater hypoxaemia. These divers have greater lung oxygen stores due to higher total lung capacity that non-diving individuals (Lindholm and Nyren 2005; Loring et al. 2007; Walterspacher et al. 2011; Ferretti et al. 2012; Patrician et al. 2021). Blood oxygen stores are dictated by blood hemoglobin concentration. This can increase only in case of red blood cell delivery into blood by spleen contraction. Some authors have suggested this possibility (Schagatay et al. 2001; Espersen et al. 2002; Baković et al. 2003). These adaptations ascribed to the mammalian diving reflex, e.g., sympathetically mediated peripheral vasoconstriction and vagally mediated bradycardia, are necessary for oxygen conservation to maintain cerebral functioning (Bain et al. 2018; Ferretti 2001; Elia et al. 2021). In defense of maintaining global cerebral oxygen delivery during prolonged breath holds, the cerebral blood flow may increase by ~100% from resting values (Elia et al. 2021). Furthermore, these divers also have greater emotional tolerance toward the desire to breathe and to resist the feeling of shortness of breath. Adaptations such as these affect NTS activity, which in turn is connected with the prefrontal cortex and limbic system through the central autonomic network. For this reason, exposure to acute levels of stress, such as during apnea, triggers emotions and feelings, which can also alter cognitive abilities. Constant exposure to these stimuli is likely to provide chronic psychophysiological adaptations such as those observed in elite divers (Diniz et al. 2014). In addition, performing pre-apnea breathing techniques that induce well-being and relaxation (Perciavalle et al. 2017) and reduce anxiety (Malathi and Damodaran 1999) and stress (Berger and Owen 1988; Netz and Lidor 2017) also contribute to greater performance and greater resistance to psychophysiological stress during apnea in elite divers (Steinberg et al. 2017). Thus, greater support for apnea is made possible by both previous physiological adaptations and pre-apnea preparation, such as a successive apnea protocol, which triggers greater physiological and psychological changes that can be observed through changes in cortical activity (Perciavalle et al. 2017).

Individuals not trained in apnea have very limited performance in this activity. The literature recognizes that performing successive apneas in the same session provides acute breaking point delay and a significant increase in maximum apnea time (Heath and Irwin 1968; Bartlett 1977; Schagatay et al. 1999), as well as in the struggle duration phase (Nishino et al. 1996). As the duration of the struggle phase is mainly influenced by the proprioceptive activity of the respiratory muscles, its prolongation seems to be related to some type of habituation or reduced sensitivity of this proprioceptive stimulus or of the hypercapnic or hypoxic ventilatory response, caused by the increase in endogenous opioids in the central nervous system, or decreased anxiety, or some other mechanism (Nishino et al. 1996). In any case, the cause of the increase in maximal breath-holding time in successive apnea protocols is unknown and may contribute to understanding the mechanisms of "air hunger" or other types of respiratory distress such as dyspnea (Nishino 2009, 2011). Therefore, we hypothesized that the protocol-induced increase in performance of successive apneas could significantly reduce the amplitude of the beta and alpha bands especially in individuals not trained in apnea or with respiratory distress (Fig. 1). In addition, a protocol of successive apneas seems to be promising for understanding the neural mechanisms of respiratory distress and dyspnea.

In this sense, interesting questions could be raised knowing that the easy phase duration does not change sharply after successive apneas (Nishino et al. 1996), for example: what results would be produced by EEG when the struggle phase time was increased? What would the activity of the prefrontal cortex and sensory cortex be like under conditions of respiratory distress, given that the prolongation of diaphragm activity influences the increase in voluntary activity sustaining the apnea up to its breaking point? What would EEG activity be like when we compare healthy individuals with respiratory restriction triggered by some apparatus or individuals with respiratory disorders, such as obstructive, restrictive, and neurological diseases under conditions of a prolonged struggle phase and respiratory distress? In addition to answering these questions, the successive maximal apnea test protocol associated with the use of electroencephalography could be used to assess cortical brain waves under conditions of irritability and anxiety triggered by exposure to the respiratory stress of air deprivation.

Conclusion

Based on the evidence in the literature, we propose that the prolongation of the maximal apnea time through a successive maximal apnea protocol is a useful method for the study of EEG adaptations under conditions of air deprivation. In addition, it expands the field of study of the determinants of dyspnea and respiratory distress based on the analysis of cortical activity.

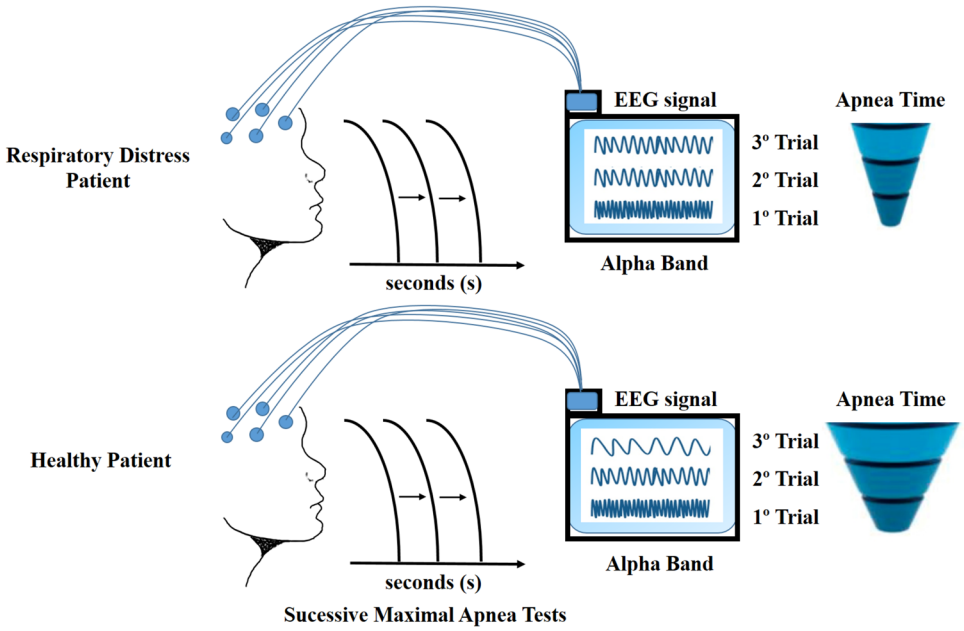

Fig. 1 Diagram representing the hypothesis of this study where the successive apnea protocol is seen on the left, with an increase in the performance in the apnea time (seconds) and the consequent reduction in the frequency in the EEG signal (right). In patients with respiratory distress, performance and adaptations in the EEG signal (alpha band) would be lower

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Declarations

Conflict of interest None of the authors has conflicts of interest to declare.

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