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Comments and Controversies

Ecological nuances in functional magnetic resonance imaging (fMRI): psychological stressors, posture, and hydrostatics

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Brain imaging techniques such as functional magnetic resonance imaging (fMRI) have forged an impressive link between psychology and neuroscience. Whereas most experiments in cognitive psychology require participants to perform while sitting upright in front of display devices, fMRI obliges participants to perform cognitive tasks while lying supine and motionless inside a narrow bore. In addition to introducing psychological and physical stressors, such as loud thumps and head restraints, fMRI procedures also alter brain hydrostatics. The ecological factors associated with current fMRI technology, such as supine posture, may skew cognitive processing and influence hemodynamic and electrophysiological measurements, especially in extreme age groups and pathological populations. Recognizing the central role of fMRI in unraveling the neural mechanisms of cognition, we outline ways to address these limitations.

Keywords: Neuroimaging; Functional magnetic resonance imaging (fMRI); Posture; Stress; Ecology; Cognition; Ergonomy

Introduction

Proponents of neuroimaging regard it as an important tool in the advancement of cognitive theories (Posner, 2003); skeptics call it the "new phrenology" (Uttal, 2001). Either way, imaging the living brain has revolutionized cognitive neuroscience and physiological psychology (Posner, 2004, in press; Posner and Raichle, 1996). As fMRI becomes ubiquitous, more books, research articles, and specialty journals are now devoted to neuroimaging (Illes et al., 2003). While we deem fMRI an important neurocognitive technique, we believe the physical conditions of fMRI introduce variables that could influence measured results. Whereas subjects in most psychological experiments sit upright in front of display devices, fMRI requires participants to perform cognitive tasks while recumbent and motionless inside the magnet's bore. This seldom-addressed discrepancy should not go unnoticed, as it may significantly influence both the acquisition and the interpretation of data.

Current fMRI technology dictates many restrictions to experimental subjects, including postural constraints and other stressors. These "ecological" factors, both psychological and ergonomic, may influence results and their interpretation (Raz et al., 2000, 2001b). For example, if these factors influence neurocognitive processing or hemodynamic parameters, blood–oxygen level-dependent (BOLD) contrast responses could change. Interpretation of fMRI data would necessarily have to account for the influence of these factors. In addition, although most healthy adults seem to endure fMRI conditions well, some do not; the scanning of pediatric, geriatric, and pathological populations presents a greater challenge (Slifer et al., 1993).

In this paper, we review some of the ecological factors intrinsic to fMRI and discuss their potential effects on cognitive processing. Specifically, we provide hydrostatic calculations suggesting that such ergonomic factors as posture affect brain hemodynamics and may influence cognitive processing. Finally, we caution that specific populations may be particularly vulnerable to these effects and outline ways to address these vulnerabilities.

Common stressors in fMRI of the human brain

An fMRI scan can be a daunting experience for the uninitiated subject, and fMRI participants may feel uneasy even prior to the actual scan. Pre-test procedures involve: meticulous screening for ferromagnetic materials, urine pregnancy tests, preliminary behavioral training, lengthy consent forms, and other detailed preparations. These procedures may influence a subject's motivation and

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induce anxiety. The magnet environment itself can be intimidating, with multiple pieces of peripheral equipment (e.g., squeeze ball, headphones, and response buttons) and at least a few staff members.

During the scan itself, participants are exposed to multiple psychological stressors (Brennan et al., 1988). fMRI sessions often span or exceed an hour, but even shorter scans can produce strain. Entering the scanner "head first," which is the case in neuroimaging, can result in much higher levels of anxiety compared to "feet first" (McIsaac et al., 1998). Feelings of anxiety can be mild initially (e.g., sweating or slight nervousness) but can escalate rapidly. Approximately 5–10% of participants in imaging studies exhibit severe panic or claustrophobia upon entering the scanner, and 30% experience some form of anxiety either during or preceding a scan (Robinson, 1996). Anxiety can trigger a variety of physiological changes, including heavy breathing, heart palpitations, changes in blood pressure, and dizziness. These effects may influence neural-metabolic function and cerebral blood flow (Brennan et al., 1988), thereby altering the BOLD signal measured by fMRI.

Subjects are positioned within a head coil while supine and motionless on a motorized bed with at least the head, if not the entire body, encased within the magnet's cramped bore. Contraction of jaw and throat muscles as well as head movements during testing may cause distortions. Neuroimagers typically apply mechanical contrivances, such as head restraints, to prevent such distortion. Participants are instructed to neither speak (except in an emergency) nor nod their heads. Instead, subjects communicate by depressing designated keys on a button pad. Furthermore, a supine posture and restricted motion, combined with the scanner's rhythmic thumping, can induce fatigue, cognitive dulling, and even sleep-conditions unfavorable to monitoring vigilant mental performance. The required supine position is known to induce drowsiness in elderly subjects and in certain pathological populations (Ray et al., 1993). Prolonged task performance also tends to increase either physical or mental fatigue. This gradual wearying likely emerges in a complex, nonlinear fashion (Liu et al., 2003), affecting both automatic and volitional processes (Doran et al., 2001; Raz et al., 2001a).

Healthy adults can usually remain calm and motionless during imaging. However, children and some psychiatric patients often lack the ability to monitor their own small movements. They also become anxious more easily and lack the ability to persevere in a task under stressful conditions. Consequently, neuroimagers must assess their subjects' ability to effectively participate prior to scanning and acclimate subjects to the fMRI environment (Slifer et al., 1993). Mock scanners, which provide simulated MRI environments for this purpose, are now commercially available. Desensitization in a mock scanner appears to greatly improve the likelihood of a successful scan. Nonetheless, the neural fingerprints of the ecology and ergonomy associated with fMRI technology may still alter the very phenomena neuroimagers wish to measure.

Some data suggest that the physical conditions of imaging affect cognitive functioning in the scanner (Charlesworth and Nathan, 1984) and interfere with optimal performance (Melendez and McCrank, 1993). Thus, imaging procedures may reflect different operationalizations of neurocognitive processes compared to those measured outside the scanner. Although a supine position is usually used in neuroimaging, posture differences within the magnet (i.e., supine vs. prone) can also affect mental and emotional states and can vary cognitive functioning (Melendez and McCrank, 1993).

fMRI scans pose ambient stressors by generating 120–135 dB of gradient noise and 1–1.5 kHz of vibration throughout a typical echo-planar imaging scan. Spiral and reverse spiral sequences, increasingly used, may be even louder (Glover and Thomason, 2004; Preston et al., 2004). Ear protection reduces noise by about 30 dB, with further reductions caused by the microphonic effect, a physical phenomenon in which the sound exposure of the subject inside the magnet is lower relative to that experienced by a person outside the bore. Even so, noise and vibration may hinder subject performance, although this disruption is usually greater at the beginning of the scan; subjects gradually acclimate.

Posture influences neurophysiology across development

In addition to psychological factors, posture can also alter physiology and thereby affect fMRI results. Posture changes influence hemodynamics. As early as infancy, human baroreceptor reflexes increase and decrease blood pressure (BP), as demonstrated using pharmacological agents and by examining spontaneous fluctuations in BP (Drouin et al., 1997; Murat et al., 1988). Heart rate (HR) responses to BP changes following shifts in posture also reflect a reflex mediated by the baroreceptors. These variations have been reported in several studies involving newborns days after birth (Andrasyova and Kellerova, 1996). These studies generally report that HR increases after head-up tilts and decreases after head-down tilts (Fifer et al., 1999). The HR changes appear to be sustained for as long as the infant remains in the new position (Thoresen et al., 1991). This finding has recently been extended to electroencephalographic (EEG) measurements. Whereas there is consensus regarding a major alpha generator in the posterior cortex (Hagemann, 2004), baroreceptor activation/inhibition in newborns not only influences EEG in the medulla and brain stem, but also alters electrical brain activity in regions of the right frontal cortex and midoccipital cortex (Grieve et al., 2003). In adults, head-up tilting results in increased EEG beta activity (12–24 Hz). While this may reflect some form of cortical arousal, recent scalp electrode event-related potentials (ERP) data show that posture affects electrical brain activity in children as well (Diamond et al., 2003; Diamond et al., in preparation). These findings agree with data showing that posture can substantially influence perfusion pressure in the brain and thus affect hemodynamics (Mavrocordatos et al., 2000).

Data from elderly individuals also suggest an interaction among posture, blood pressure, and cognitive performance (Matsubayashi et al., 1997; Perlmuter and Greenberg, 1996). These data indicate that elderly persons with postural hypotension/hypertension score lower on cognitive tests than those without postural hypotension/hypertension. In these individuals, low beta activity following postural changes predicts cognitive decline. These findings accord with the idea that postural restrictions imposed by fMRI scans may affect cerebral blood flow and subsequent cognitive performance in older individuals.

Evidence also suggests that additional resources are required to maintain postural stability in old age (Maylor and Wing, 1996). Attentional control seems to play a role in the relationship between posture and cognitive performance (Teasdale et al., 1993). In fact, with increasing cognitive demands, posture, and attention become more difficult for the elderly to maintain (Woollacott and Shumway-Cook, 2002). Although cognitive variation between the upright and recumbent positions is most prominent in infants (Pecheux, 1996) and the elderly (Brauer et al., 2002), fMRI posture changes respiration in all individuals regardless of age by altering diaphragm function (Rehder, 1998). This change in functional residual capacity influences both cognitive processes and blood oxygen levels, and may thereby skew fMRI data, albeit more so for extreme age groups.

Physiology and blood flow

The idea that changes in blood flow in the brain may result from local neurofunctional changes is not new. William James (1890) reported such accounts by the 19th-century physiologists Roy, Sherrington, and Mosso. Within the vascular system, blood flow (BF) and BF velocity (BFV) fluctuate greatly as a function of physiological factors (e.g., blood pressure, vessel diameter, blood density, and gaseous composition) and physical factors (e.g., individual's health, size, age, and fitness). Researchers typically study BFV in laboratory animals and report such measurements as rough estimations because the technique used can influence the results. Nonetheless, minute variations in vessel diameter can instigate large changes in BF (i.e., perfusion or volume per unit time). This occurs because BF, which is proportional to the pressure gradient between the two ends of the vessel divided by its resistance to flow, is also proportional to a polynomial expressing vessel radius as a parameter raised to the 4th power.

Researchers have used the laboratory rat to study the relationship between sensory stimulation and local BF changes. Stimulation of the sciatic nerve causes increases in both diameter and flow in the somatosensory cortex without affecting the mean arterial blood pressure (Ngai et al., 1988). Another study showed that electrical stimulation of parallel fibers in the rat cerebellum induces focal brain activations and causes over 25% arteriole dilation in the vascular bed supplying the activated neurons. In larger arterioles upstream, diameter increases by about 8% (Iadecola et al., 1997). These results show that BF can increase in vessels upstream of the local neuronal activity. Moreover, data from non-human primates suggest that central dopaminergic and noradrenergic neurons could influence BF independently of local neuronal activity, perhaps in response to such contexts as stimulus-response conditioning (Krimer et al., 1998). Hence, the BOLD signal may not strictly reflect the energy needs of active neurons. Instead, BF changes may be associated with protracted changes in MRI signal. Stress and posture may well be such underlying factors.

Orthostatic factors: standing erect, sitting upright, and lying down

Using a portable gantry positron emission tomography (PET) system, researchers have examined brain hemodynamics as a function of various postures (Ouchi et al., 1999). Standing with feet together activates the cerebellar anterior lobe and right visual cortex (Brodmann area 18/19), yet standing on one foot increases cerebral blood flow in the cerebellar anterior vermis and parts of the posterior lobe ipsilateral to the weight-bearing side. Standing with feet together is accompanied by activation within the visual association cortex and the anterior and posterior vermis as well as within the midbrain, whereas standing with the eyes closed activates the prefrontal cortex (Brodmann area 8/9). Reaffirming the central role of the cerebellar vermis in maintaining an erect posture, these results demonstrate how posture can influence neuroimaging results and suggest that certain brain areas (e.g., visual association cortex) may subserve postural regulation while erect.

Additional PET data examining regional cerebral blood flow (rCBF) in three different orthostatic conditions show that an upright posture changes hemodynamic parameters in healthy middle-aged humans (Ouchi et al., 2001b). Despite unchanged physiological data, both absolute and relative rCBF levels are significantly elevated in the cerebellar vermis in the standing position compared with levels measured in the supine and sitting postures. However, rCBF levels in the frontal and parietal cortices are lower in the sitting and standing positions than in the supine position. The data also address chronological age effects, indicating that standing rCBF measurements inversely correlate with age. Investigation into the effects of posture on brain hemodynamics has also been extended from healthy volunteers to patients. PET data from 22 individuals with a minor stroke show significant rCBF reductions while sitting, which inversely correlates with oxygen metabolism (Ouchi et al., 2001a). Based on these findings, it seems that the cerebellum's role in postural control involves greater activity of the vermis when standing upright compared with either sitting or lying supine.

Neurohydrostatics of posture

Cerebral perfusion pressure, defined as mean arterial pressure minus intracranial pressure (ICP), can change considerably as a function of posture in both animals and humans (Brosnan et al., 2002; Mavrocordatos et al., 2000). These changes stem from differences in the hydrostatic pressure component of the ICP surrounding the vascular bed. Assuming an average brain width of 140 mm, an average brain length of 167 mm, and an average brain height of 93 mm for a 150-lb human, we can calculate the hydrostatic component of the ICP. For example, when a person stands upright, the ICP surrounding the vascular structures at the top of the brain is about 7 mm Hg less than the ICP surrounding vascular structures at the skull's base. This value is based on the assumption that the specific gravity of the cerebrospinal fluid, ρ, is about 1.005 g/cm^3; the distance between the top and bottom of the brain, h, is about 9.3 cm; and the gravitational acceleration, g, is 981 cm/s^2:

$$P_h = \rho g h = 9168.9 \text{ dynes/cm}^2 = 6.88 \text{ mm Hg}$$

Note that 1333.2 dyn/cm^2 = 1 mm Hg. Similarly, replacing the height of 9.3 cm with a brain height of 16.7 cm, when a person is in the supine position, the hydrostatic component of the pressure in the occipital region of the brain can be 12.3 mm Hg higher than in the prefrontal area. Fig. 1 illustrates graphically the hydrostatic pressure as a function of head posture.

The hydrostatic component of normal ICP (excluding the hydrostatic component) in adults (5–10 mm Hg) creates a substantial gradient around the cerebral vasculature. (Vespa, 2003). While the hydrostatic component exerts little influence on cerebral arteries, the mean internal pressure in those arteries is much higher than the ICP (e.g., about 80–100 mm Hg) (Vespa, 2003). This is not the case for veins, in which transmural pressure may become negative. Consequently, the differential compression exerted on the venous side is substantial. Veins exposed to the differing external pressure are compressed to different degrees, causing dissimilar flow resistances. Regional blood flow in the brain can therefore be influenced by the hydrostatic pressure gradient of the ICP. Regions exposed to a low hydrostatic pressure offer less resistance to flow than do regions exposed to high hydrostatic pressure. (This model of

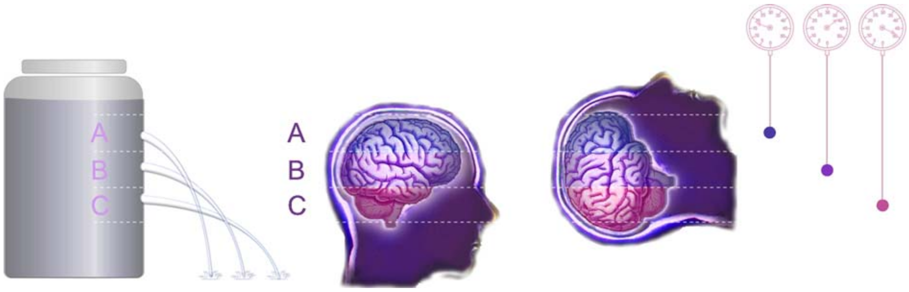

Fig. 1. Variation in hydrostatic pressure at different brain regions as a function of imaging posture.

blood perfusion dynamics is conceptually akin to West's three-zone model of the lung (West et al., 1964). In this model, lung zones are defined according to their vertical level, with zone 1 at the top and zone 3 at the base of the lungs. Zone 3 contains a higher internal hydrostatic pressure, causing dilation of the vascular bed and reduction of its resistance. Therefore, a larger portion of lung perfusion occurs in zone 3 than in zone 1.)

The influence of external pressure on flow through collapsible tubes has been described in numerous theoretical articles, as well as through in vitro and in vivo testing. Pulmonary circulation provides a particularly useful model, as it is amenable to hemodynamic measurements (Fung, 1984). A pressure differential, where the pressure around a collapsible tube (e.g., a vein) is higher than the internal pressure, can cause tube collapse and consequently augment its resistance to blood flow. Thus, when a person stands erect, the distribution of the hydrostatic pressure in the ICP is different from the recumbent position. For example, in the supine position, the hydrostatic pressure is higher in the posterior part of the brain (i.e., occipital area) than in the anterior region of the brain (i.e., prefrontal area). The distribution of blood flow in these brain regions will differ from the diffusion pattern seen when the subject is either standing or sitting upright, where the hydrostatic pressure gradient is oriented from inferior to superior regions of the brain.

fMRI of non-human primates

Scanning non-human primates allows scientific investigation into the neurophysiological substrates of BOLD fMRI and permits fruitful comparisons between human and monkey fMRI data (Kourtzi et al., 2003; Nakahara et al., 2002). However, unlike fMRI studies with humans, the first exploratory studies using fMRI of non-human primates (fMRINHP) constrained the animals into a prone, not supine, position (Dubowitz et al., 1998; Stefanacci et al., 1998). Subsequent fMRINHP explorations have afforded different scanning postures than those in human fMRI, including sitting up in a cylindrical chair (Logothetis et al., 1999) and even in the upright position using a custom-designed vertical-bore 7 T magnet and coil (Merkle et al., 2002; Pfeuffer et al., 2002). These vertical approaches may offer greater feasibility for imaging non-human primates. However, they likely introduce similar ecological wrinkles as evidenced in human imaging, particularly when studying a non-erect monkey species, such as *macaca mulatta*, in the erect position (Pfeuffer et al., 2002).

fMRINHP also opens the prospect of administering exogenous highly paramagnetic contrast agents (e.g., monocrystalline iron oxide nanoparticles, or MIONs, currently not FDA-approved in humans) to increase the signal-to-noise ratio (Leite et al., 2002). Whereas BOLD labels central blood oxygenation regulated by flow, MION labels cerebral blood by volume. Researchers can gain neurophysiological insights into the monkey brain through volume measurements, with the hope of relating monkey data to human findings through flow measurements. Nonetheless, the ecological constraints imposed on both humans and non-human primates are not typically factored into the interpretation of these results. As neuroimagers begin to draw comparisons bridging the 25-million-year evolutionary gap that separates humans from monkeys, we believe that the ecological limitations of fMRI must be addressed.

ERP and fMRI

Complementing the excellent temporal resolution of ERP with the high spatial resolution of fMRI, researchers have developed ways to relate these two measurements using mathematical models (Kiebel and Friston, 2004; Scherg and Berg, 1990). Theoretical objections aside, it is easy to overlook that electrophysiological and fMRI measurements, even when collected from the same individual, typically rely on data acquired at two different times within two dissimilar experimental contexts. Unlike fMRI, ERP usually involves subjects sitting upright. Yet an implicit assumption—that identical cognitive mechanisms and neural substrates function during the two separate experimental sessions—has not been established. Moreover, we have suggested that such an underlying assumption is unlikely to hold true (Raz et al., 2000, 2001b). Subsequent follow-up work has revealed that, at least in children, posture influences ERPs (Diamond et al., 2003). In fact, recent ERP collected from 5- and 8-year-old children both sitting upright and lying down in a mock scanner revealed two non-interacting effects (Diamond et al., in preparation). First, ERP patterns of neural activity varied as a function of posture. Second, significant differences were apparent as a function of whether children were able to see their hands (proprioception).

These ERP differences might arise from obtaining the electrophysiological signal with the subject lying down rather than from actual brain changes. For example, electrodes may not record optimally in certain postures. However, this is unlikely, as personal communications from various laboratories using different equipment report similar findings (e.g., Brandeis, 2004, personal communication; Doran et al., 2001). These sparse accounts suggest that EEG and even ERP patterns may be different when subjects are erect compared with recumbent. Hence, recent efforts to acquire simultaneous ERP and event-related fMRI data are accordingly hampered by postural constraints (Logothetis, submitted for publication).

Beyond the subtraction method

Most fMRI assays are based on the "subtraction method" (Donders, 1969). In fMRI, the BOLD signal produced by a cognitive operation is computed as the difference in signal between two tasks that differ only by the cognitive operation of interest. The control is therefore subtracted from the experimental condition. Beyond a theoretical critique (Friston et al., 1996), however, the notion that the subtraction method accounts for the aforementioned ecological and postural caveats is inaccurate for a number of reasons.

First, researchers have not shown that the fMRI signal difference measured in humans standing erect or sitting up is comparable to that seen when supine. We have provided ample arguments suggesting that this is, in fact, improbable. The brain's physical properties (i.e., "efficiency" and "state") during the scan are not comparable with those seen during common erect wakefulness. Second, cognitive processes are probably engaged differently as a function of fMRI-induced posture and stress. This phenomenon could potentially affect the cognitive process of interest or hinder its detection. These differences may be more pronounced in certain tasks (e.g., tapping spatial operations or involving proprioception) and in susceptible populations (e.g., children, elderly, or patients), but are limited to neither. Third, fMRI data may be obfuscated because motionless supine individuals tend to drift naturally into a more somnolent state over time. Evidence shows that EEG, ERP, and ICP all change as a function of posture (Diamond et al., 2003, in preparation; Grieve et al., 2003; Mavrocordatos et al., 2000). Finally, all of these factors could significantly interact at various time points throughout fMRI scans.

Concluding remarks

We have outlined ergonomic and hydrostatic accounts showing that subjects in fMRI experiments undergo psychological and physical conditions that may alter neural activity. These effects may influence both cognitive processing and brain hemodynamics and thereby change the BOLD signal as well as EEG and ERP. We do not wish to disparage the value of recumbent neuroimaging or the importance of fMRI technology in unraveling the substrates of cognition. Instead, we want to illuminate some often-ignored caveats to fMRI measurements. While other potential complications for fMRI results exist (e.g., the effects on brain hemodynamics of commonly used blood thinners, such as aspirin, vasoconstrictors, such as caffeine, or psychiatric drugs, such as fluoxetine), we believe that the factors discussed have the greatest potential to skew outcomes.

At present, all scanners used on humans are horizontally oriented. Although vertical fMRI scans are desirable, it may take time before such scanners become available for research with humans. And whereas fMRI assays have begun to explore upright positions in non-human primates, their associated ecological constraints still negatively affect the interpretation of these data. As neuroimagers increasingly scan developmental and clinical populations, ecology and ergonomy may hold substantial hemodynamic consequences.

Associated fMRI procedures can influence performance. Compounded by individual differences (Fan et al., 2003), the overall impact of the fMRI environment seems to increase general variance. As is the case with clinical populations, increased variance decreases the power of detecting population effects and promotes within-group analyses (Kosslyn et al., 2002). Also, ecological and hydrostatic factors associated with fMRI procedures may activate different cognitive processes. These activations may alter the cognitive process of interest or encumber its isolation. Finally, hydrostatic factors may influence the brain hemodynamic response, particularly along the prefrontal-occipital gradient.

Aside from advocating vertical human fMRI scanners, we propose three chief ways to manage these concerns. First, we reemphasize the importance of converging evidence via a process of triangulation: data acquired using different methodologies should complement fMRI results and thereby address these caveats. Second, we encourage researchers to use mock scanners before fMRI sessions to reduce subjects' stress levels and to collect non-fMRI data while subjects are supine for consistency. Third, we recommend the careful crafting of analytical tools that would permit parameterized correction of brain hemodynamics based on hydrostatic and postural considerations. These adjustments would predominantly apply to flow parameters in the prefrontal and occipital brain regions when subjects are supine and can be estimated using mathematical models. Also, research into human brain vasculature and hemodynamics should provide physiological data to better inform such models. We hope to soon report experimental data as well as a rigorous model addressing this point.

We are in the midst of an ever-rising interest in neuroimaging. Magnets are rapidly sprouting up in research centers around the world, and fMRI images are promulgated in mainstream media. However, both researchers and clinicians would do well to temper their interpretations of findings, mainly as they pertain to developmental and pathological populations, by considering the extant ecological caveats intrinsic to this powerful technique.

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