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Review

The Stroke-Migraine Depolarization Continuum

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The term spreading depolarization (SD) refers to waves of abrupt, sustained mass depolarization in gray matter of the CNS. SD, which spreads from neuron to neuron in affected tissue, is characterized by a rapid near-breakdown of the neuronal transmembrane ion gradients. SD can be induced by hypoxic conditions—such as from ischemia—and facilitates neuronal death in energy-compromised tissue. SD has also been implicated in migraine aura, where SD is assumed to ascend in well-nourished tissue and is typically benign. In addition to these two ends of the "SD continuum," an SD wave can propagate from an energy-depleted tissue into surrounding, well-nourished tissue, as is often the case in stroke and brain trauma. This review presents the neurobiology of SD—its triggers and propagation mechanisms—as well as clinical manifestations of SD, including overlaps and differences between migraine aura and stroke, and recent developments in neuromonitoring aimed at better diagnosis and more targeted treatments.

Introduction

Spreading depolarization (SD) is the generic term for waves of abrupt, sustained mass depolarization in gray matter of the CNS (Dreier, 2011; Somjen, 2001) resulting from near-breakdown of the neuronal transmembrane ion gradients (Hansen and Zeuthen, 1981; Kraig and Nicholson, 1978; Mutch and Hansen, 1984; Windmüller et al., 2005). The wide array of electrochemical changes involved in SD indicates that this is among the most fundamental processes of brain pathology (Table 1). The question of whether SD occurs in humans remained controversial for decades, despite its detection in the brains of virtually all species examined, including invertebrates such as locusts and cockroaches. Its pioneer investigator, the Brazilian neurobiologist Aristides Leão, had specifically linked SD to migraine aura and cerebral ischemia (Leão, 1947; Leão and Morison, 1945). His hypothesis is an outstanding example for a counter-intuitive hypothesis on brain pathology based on laboratory experiments, that only six decades later and after enormous resistance from the clinical community was eventually confirmed in clinical studies.

Over the last decade, it became possible to electrocorticographically (ECoG) record SDs in patients with acute cerebral injuries such as traumatic brain injury (TBI) and stroke (cf. http://www.cosbid.org) (Dohmen et al., 2008; Dreier et al., 2006, 2009; Fabricius et al., 2006; Hartings et al., 2011a, 2011b; Strong et al., 2002). Advanced neuromonitoring has increasingly become routine practice in neurointensive care as it may offer unprecedented opportunities for diagnosis and treatment. In parallel to its advantages, this more widespread collection of data presented new challenges, as clinicians are more frequently confronted with the entire SD spectrum, rather than the two extremes of SD in either severely ischemic or normal tissue. This continuous depolarization spectrum is furthermore reflected by clinical overlaps between migraine with aura and stroke. It is referred to as the stroke-migraine depolarization continuum based on Leão's original observations, his translational hypotheses (Leão, 1947; Leão and Morison, 1945), and the accumulated evidence from research over the past half century.

The first part of this review presents the neurobiology of SD, including overlaps between migraine aura and stroke models. The second part is devoted to patients' percepts when SDs sweep across their brains. Reconciling the concepts of SD in migraine aura versus stroke presents an ongoing challenge: Can these two pathologies share a similar fundamental phenomenon given that the patients' percepts are so different? A possible solution to this enigma may emerge from observations of two fundamentally different types of depression in spontaneous activity that can be associated with SD. We also discuss and clarify the neurophysiological differences between "depression" and "depolarization." Although these terms are often used interchangeably, awareness of the distinction between them is crucial for understanding their clinical implications.

Part I: Neurobiology of SD

Electrochemical cells, such as found in electric batteries, convert stored chemical energy into electric energy. Neurons, like batteries, store chemical energy in the form of ion gradients across the cell membrane, the most important ions being potassium, sodium, calcium, and chloride. Energy stored up in these ion gradients can be used by neurons to generate electric signals. During electric signaling, the electric gradient across the cellular membrane changes, but not the ion gradients between the bulk solutions on both sides of the membrane; this is because only a very small absolute number of ions crosses the membrane to transiently discharge and recharge it (Alle et al., 2009). Hence, a physiological signal consumes only a negligible fraction of the total electrochemical energy stored up in a neuron (Dreier et al., 2013a).

But what happens when ATP is persistently depleted from the tissue? At rest, sodium and calcium continuously leak into cells and potassium leaks out of them. These movements are driven

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Table 1. Ion Changes during IEEs and SD Based on Dreier et al. (2013a)

	Physiological State	IEE	SD
$[K^+]_i$ (mM)	134	126	106
$[K^+]_o$ (mM)	2.3–3.1	10–12	35–60
$[Na^+]_i$ (mM)	10	16	35
$[Na^+]_o$ (mM)	146–154	135–143	57–59
$[Ca^{2+}]_i$ (μM)	0.06	0.13	25
$[Ca^{2+}]_o$ (mM)	1.2–1.3	0.8–1.0	0.08
$[Cl^-]_o$ (mM)	145–148	151–154	95
Extracellular space (%)	18–22	14	5–9
Negative intracortical DC shift (mV)	0	2–4	5–30
Sustained negative membrane potential (mV)	60–70	40–45	1–17

Box 1.

Within minutes of cerebral ischemia, decline of the apparent diffusion coefficient (ADC) of water is observed in MR images. ADC decline reflects beading of neuronal processes. Beaded morphology allows a larger volume to be encompassed within an equivalent surface area, causing decreased mobility of intracellular water (Budde and Frank, 2010). SD is the mechanism underlying abrupt dendritic beading in the cortex and basal ganglia. Accordingly, time-locked to SDs, dendritic beading shows waxing and waning in the penumbra before it eventually persists (Risher et al., 2009, 2010). Moreover, SD initiates a rapid ADC drop both in healthy and ischemic gray matter (de Crespigny et al., 1999). Beading is also of therapeutic interest. Pharmacological inhibition of beading protected dendrites from ischemic injury (Risher et al., 2011).

by the release of Gibbs free energy. When ATP is depleted, ATP-dependent membrane pumps such as the Na,K-ATPase fail to restore the leaking ions. As a result, all mammalian cells are inevitably impacted adversely by a toxic run down in the ion gradients before they die. This is reflected in a sustained depolarization of the cellular membranes.

In non-neuronal tissues this process is fortunately slow, often allowing a treating physician sufficient time to intervene (Somjen, 2004). The neocortex by contrast, under pathological conditions shows sustained depolarizations which happen abruptly. The quick onset is followed by a plateau phase of a new polarization level, which in turn may or may not be followed by recovery. Two fundamental spectra of such abrupt sustained depolarizations have been described: (1) the spectrum of ictal epileptic events (IEE), which despite their dramatic associated changes in neural firing are characterized by relatively mild sustained depolarization (Table 1); and (2) the spectrum of SDs, characterized by sustained near-complete depolarization.

At a given tissue spot, the near-complete breakdown in ion gradients during SD happens rapidly, within ~6–8 s, and lasts locally for at least 30 s. Ion changes of this magnitude never occur under other conditions in living neurons. As an example for the ion concentration changes during SD, in dendrites, the intracellular calcium may surge up to 25 μM, a level which is toxic when the recovery from SD is hindered as in metabolically compromised tissue (Aiba and Shuttleworth, 2012; Dietz et al., 2008). The ion changes lead to intracellular hyperosmolality (Kraig and Nicholson, 1978). The resulting water influx causes cytotoxic edema and shrinkage of the extracellular volume fraction from 20% to ~5% (Mazel et al., 2002; Vorísek and Syková, 1997; Windmüller et al., 2005). This is observed as swelling of neuronal somata and focal dendritic enlargement and constriction ("beading") (Murphy et al., 2008; Risher et al., 2009, 2010; Takano et al., 2007) (Box 1). Moreover, neuronal mitochondria depolarize (Bahar et al., 2000), and neurotransmitters such as acetylcholine, γ-aminobutyric acid (GABA), and glutamate are released in large amounts (Fabricius et al., 1993; Zhou et al., 2013). Endogenous GABA may have a janus-faced role as $GABA_A$ receptor activation limits the propagation rate (Aiba et al., 2012), but may, on the other hand, facilitate cell swelling through chloride entry (Allen et al., 2004). This contrasts with glutamate, whose primary effect is facilitation.

SD has been found in virtually all gray matter. However, in the olfactory bulb, brain stem, and spinal cord, it can only be provoked in presence of conditioning media (Somjen, 2001). Also, some cortical areas such as retrosplenial cortex are more resistant to SD (Leão, 1944). This region-specific protection is age-dependent. Thus, the immature brainstem can transiently generate SD in absence of conditioning media (Richter et al., 2003). In white matter, SD does not occur.

SD is observed as a large negative potential change in the direct current (DC) frequency range (less than ~0.05 Hz) of the ECoG (cf. DC-ECoG traces in Figure 1). This DC shift emanates from differences in depolarization between soma and dendrites (Canals et al., 2005). Because the DC shift is generated by neurons, it is observed not only in vivo but also in brain slices even though these lack an intact blood-brain barrier (BBB); this contrasts with BBB-generated DC shifts, which are potential confounders during in vivo recordings (Kang et al., 2013).

Another hallmark of SD is its slow spread, at ~2–8 mm/min. The slowness suggests a reaction/diffusion mechanism in which neurons release neuroactive substances such as glutamate and/or potassium. These diffuse to adjacent neurons, where they trigger a self-propagating regenerative process. The exact propagation mechanism is unknown. Rise in extracellular potassium precedes all other ion changes in the bulk solutions during SD, but microelectrode recordings suggest that it does not precede the neuronal depolarization (Canals et al., 2005; Hansen and Zeuthen, 1981; Herreras and Somjen, 1993a; Lehmenkühler, 1990; Somjen, 2001). A propagation model based on regenerative glutamate release via NMDA receptor activation (Zhou et al., 2013) faces the problem that indirect calcium release from mitochondria seems insufficient for driving this process in naive tissue as, in contrast to slices exposed to brief potassium challenges, removal of extracellular calcium or inhibition of voltage-gated calcium channels blocked SD in naive tissue (Dietz et al., 2008; Jing et al., 1993; Peters et al., 2003). A transcellular pathway for the reaction/diffusion via neuronal gap junctions (Herreras et al., 1994) is also questionable as gap junctions in adult animals are common between interneurons where they

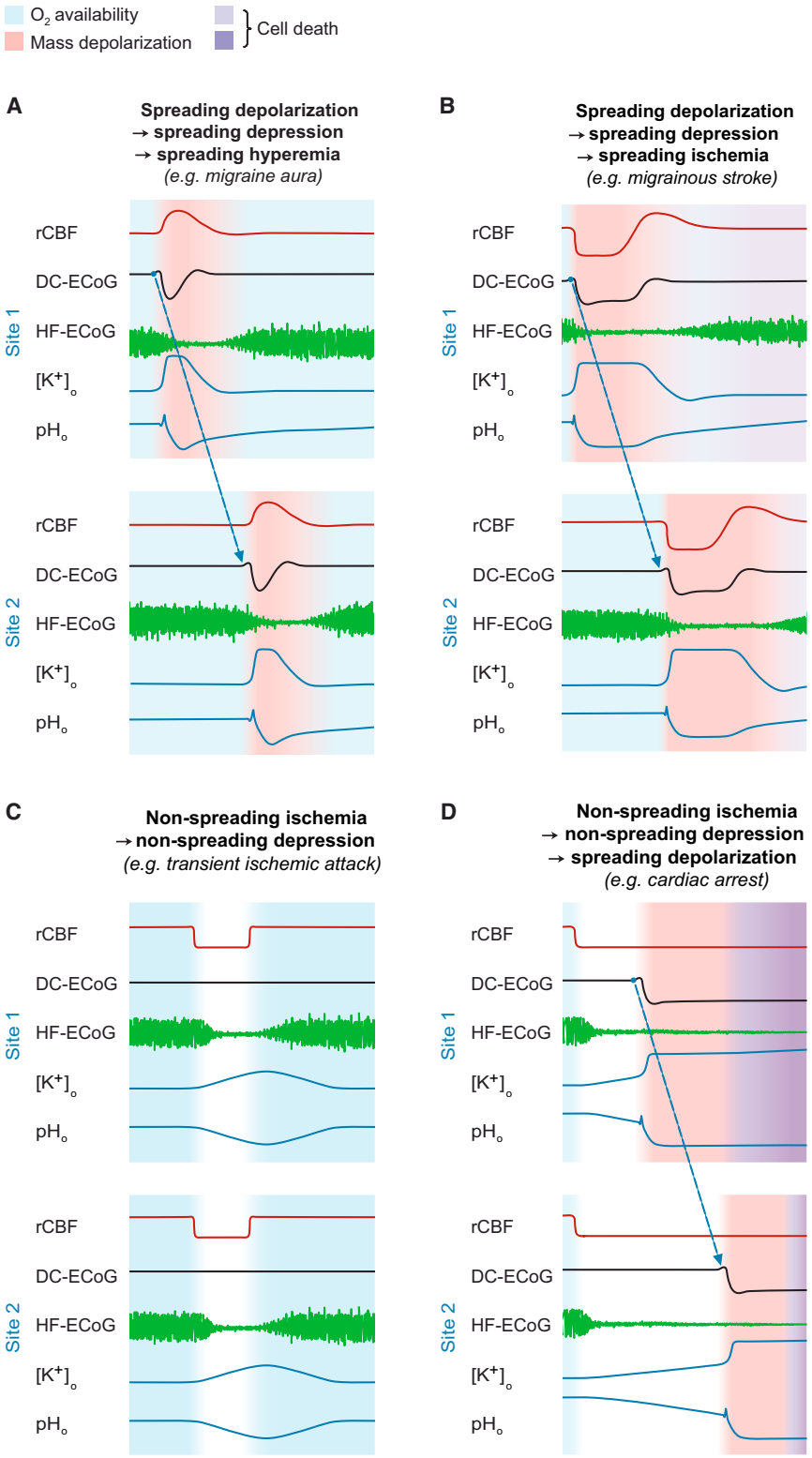

Figure 1. Pathophysiological Correlates of Common Neurological Syndromes

(A) The pathophysiological correlate of migraine aura is characterized by a large negative DC change indicating SD (DC-ECoG) that propagates at a rate of ~3 mm/min. SD initiates spreading depression of activity in the high-frequency band of the ECoG (HF-ECoG). Moreover, it triggers spreading hyperemia (rCBF) followed by a relatively subtle oligemia. Spreading depression of activity translates into the symptoms of migraine aura.

(B) Migrainous stroke starts with migraine aura in a patient having previously harmless migraine with aura. The trigger could be non-vascular. The presumed pathophysiological correlate is characterized by a negative DC change that initiates spreading depression of activity (high-frequency (HF)-ECoG) and induces spreading ischemia (rCBF), rather than spreading hyperemia, due to disturbed vascular reactivity (Dreier, 2011). The flow decline leads to a repercussion on the negative DC shift which becomes longer-lasting compared to the one in (A). If sufficiently prolonged, SD may lead to cell death under this condition.

(C) Short-lasting nonspreading ischemia due to transient middle cerebral artery occlusion (MCAO). Usually, focal ischemia is nonspreading and initiates nonspreading depression of activity (HF-ECoG) in the malperfused zone within seconds. Short-lasting, transient nonspreading depression of activity translates into a sudden and simultaneous, fully reversible neurological deficit in different modalities such as language, motor or visual function typical of a transitory ischemic attack. Also note the gradual decrease of extracellular pH (pH_o) and the gradual increase of extracellular potassium ($[K^+]_o$) that start shortly after onset of ischemia.

(D) A cardiac arrest entails nonspreading global ischemia which leads rapidly to nonspreading depression of activity (HF-ECoG). Isoelectric nonspreading depression is followed by SD after ~1–4 min (Dreier, 2011). In this case, the SD is not accompanied by spreading depression of activity because the activity has already ceased when the SD starts. If the global ischemia persists, the SD will be terminal and cells will die.

Of note, all four conditions represent prototypes.

can form dense and far-ranging networks (Fukuda et al., 2006), but are restricted to early development between pyramidal cells (Sutor and Luhmann, 1995). Ephaptic mechanisms could contribute to the propagation, as calcium drops extracellularly from ~1.3 mM to ~0.08 mM (Haas and Jefferys, 1984; Hansen and Zeuthen, 1981; Windmüller et al., 2005), but the calcium drop only happens ~4 s after the neuronal depolarization (Hansen and Zeuthen, 1981; Herreras and Somjen, 1993a; Kraig and Nicholson, 1978; Lehmenkühler, 1990).

Thermodynamic Changes

During SD, ion gradients change from the physiological double Gibbs-Donnan steady state toward a new steady state close to a simple Gibbs-Donnan equilibrium (Kraig and Nicholson, 1978; Windmüller et al., 2005). This implies that sodium and calcium enter neurons in large amounts whereas potassium exits them. The potassium outflux, however,

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is smaller than the sodium influx. Chloride follows sodium which produces an apparent anion gap, but electro-neutrality seems to be maintained by efflux of small organic anions. Based on simple models of the neuropil, changes in cation concentrations and electric field alone resulted in a Gibbs free energy release of 19–22 J/l per tissue volume (Dreier et al., 2013a). Consequent transition to cell death led to an additional small free energy release of ~2.5 J/l. The Gibbs free energy released is converted to heat. Based on the estimates above, tissue temperature should rise by ~5 mK in the front of SD. This is only slightly smaller than the measured temperature rise between 5 and 30 mK in isolated retinae of bullfrog and toad (Tasaki and Byrne, 1991). Thermodynamically therefore, SD is a state of living neurons, in which 90% of the Gibbs free energy contained in the ion gradients is lost ("free energy starving"). Neurons fall into this state in various conditions such as migraine aura, stroke, TBI, hypoxia, and hypoglycemia. From there, they either recover or die. Notably, during IEEs, the loss of Gibbs free energy is much smaller than during SDs and only amounts to ~2.8 J/l.

The Role of Na,K-ATPase

The Na,K-ATPase provides outward transport of sodium in exchange to potassium, thereby consuming ~50% of the brain energy. It critically supports several vital processes, including reuptake of neurotransmitters such as glutamate, uptake of other amino-acids and carbohydrates, and Na,Ca-antiport. Na,K-ATPase counteracts SD in two ways: it opposes triggers of SD by support of glutamate removal from the extracellular space and potassium buffering, and it is critical for the recovery from SD. Activation of the NA,K-ATPase consumes energy. Therefore, tissue ATP declines by ~50% not only in energy-deprived but also in well-supplied tissue during SD (Mies and Paschen, 1984).

In the rodent brain, there are three different Na,K-ATPase isoforms: α_1, expressed by all cells; α_2, mainly expressed by astrocytes in the adult brain; and α_3, exclusively expressed by neurons. The α_2 and α_3 isoforms can be distinguished from the α_1 isoform by their higher affinity to ouabain. Ouabain only triggers SD when all three isoforms are inhibited. Complete inhibition of α_2 and α_3 with partial inhibition of α_1 causes a cluster of recurrent SDs, whereas complete inhibition of all isoforms causes terminal SD (Balestrino et al., 1999). Selective reduction of activity of specific α isoforms may lower the threshold of SD. This was investigated using electric stimulation to trigger SD in genetically engineered mice carrying the human W887R mutation in the ATP1A2 orthologous gene, which results in retention of the mutant α_2 isoform in the endoplasmic reticulum, with subsequent proteasomal degradation and loss of function (Leo et al., 2011). In patients, mutations in the ATP1A2 gene cause familial hemiplegic migraine type 2 (FHM2), which is clinically characterized by complicated forms of migraine aura (De Fusco et al., 2003). Functional testing indicated that the putative pathogenetic effect of the mutations results from loss of function in a single allele of ATP1A2. Consistent with the SD hypothesis of migraine aura, heterozygous $ATP1A2^{+/R887}$ mutant mice showed both increased propagation velocity and reduced electric threshold for SD in vivo (Leo et al., 2011). This results from enhanced glutamatergic transmission. In adult somatosensory cortex, the α2 isoform almost completely co-localizes with the astrocytic glutamate transporters GLAST and GLT1 (EAAT1, EAAT2). Analysis at the ultrastructural level revealed that this complex occurs preferentially in astrocytic processes around asymmetric glutamatergic synaptic junctions, but not around GABAergic terminals (Cholet et al., 2002). Insufficient buildup of sodium and potassium gradients in this subcellular microdomain presumably slows down glutamate reuptake, thereby increasing glutamate in the synaptic cleft. Interestingly, a mutation in SLC1A3, encoding the astrocytic glutamate transporter GLAST (EAAT1), was reported to cause clinical features resembling FHM (Jen et al., 2005).

Triggers of SD

Based on computer simulations, Kager et al. (2002) suggested that the actual SD process starts when neuronal cation outflux (via ATP-dependent membrane pumps and potassium channels) fails to compensate for influx of sodium and calcium; as a result, the net flux across the membrane turns inward and persists in that direction. Channels mediating the net inward current need to be voltage-gated and/or dependent on extracellular potassium to be able to initiate the positive feedback cycle that confers to SD's all-or-none characteristics. Chloride conductances may counteract this (Aiba et al., 2012).

SD triggers can be roughly categorized into two major groups: (1) those depolarizing neurons by sodium and/or calcium channel activation, and (2) those depolarizing neurons indirectly by Na,K-ATPase activity reduction (Somjen, 2001). Examples of (1) are IEEs, glutamate, potassium, and veratridine. Examples of (2) are conditions of ATP-depletion such as ischemia, hypoxia, and hypoglycemia, as well as direct inhibition or functional disturbance of Na,K-ATPases by drugs such as ouabain or palytoxin. SD can also be triggered by minimal trauma. Other examples of particular interest for (2) (Na,K-ATPase activity reduction) are brain topical superfusion of the vasoconstrictor endothelin-1 (ET-1) (Dreier et al., 2002, 2007), or injection of air microemboli, polystyrene microspheres, or cholesterol crystals into the carotid circulation (Nozari et al., 2010), which trigger short-lasting SDs through mild ischemia. In the case of air microemboli, the duration of ischemia was insufficient to cause infarcts whereas the other procedures typically resulted in tiny cortical microinfarcts of 100–200 μm in diameter, which is below resolution of a 9.4 T animal magnetic resonance imager (MRI). In view of their origin, and although short-lasting, these SDs are so-called anoxic SDs.

Anoxic SD

Extracellular parameters can be used to distinguish between short-lasting anoxic SD in mildly ischemic tissue and SD of almost similar duration in well supplied tissue. Two particularly useful indicators are the mild acidosis (Hansen and Lauritzen, 1984; Oliveira-Ferreira et al., 2010; Taylor et al., 1996) and the gradual rise in potassium (Dreier et al., 2002; Erdemli et al., 1998; Müller and Somjen, 2000a; Nedergaard and Hansen, 1993) that precede only anoxic SD ($[K^+]_o$ and pH_o traces in Figures 1C and 1D compared to those of Figure 1A). Also, spontaneous release of neurotransmitters, such as GABA and glutamate, is significantly increased specifically before anoxic SD (Allen et al., 2004; Fleidervish et al., 2001). Moreover, under oxygen-glucose deprivation, arrival of SD was associated in mouse brain slices with a large calcium rise up to ~25 μM that starts in

the soma and quickly travels toward the apical dendrites. By contrast, in well-supplied tissue, SD produces a short calcium rise of ~8 μM in soma and 25 μM in apical dendrites followed by an advancing front of high calcium that progresses from distal dendrites toward the soma (Dietz et al., 2008). Furthermore, removal of extracellular calcium prevents SD in well supplied tissue but not in hypoxic one (Dietz et al., 2008; Peters et al., 2003). Sodium conductances seem more important than calcium conductances for anoxic SD, as substitution of sodium by membrane-impermeant cations is sufficient to block anoxic SD (Müller and Somjen, 2000b). However, similar to SD in well supplied tissue, the ion conductances involved in maintaining the depolarization phase are not sodium-selective, as the depolarization remains below zero and the whole-cell current reverses at a slightly negative level (Somjen, 2001). Failure of the energy-dependent recovery under continued oxygen depletion is the most obvious discriminator between anoxic SD and SD in well-supplied tissue. This feature renders the negative DC shift duration a useful measure for the local tissue energy status, indicating the risk for neuronal damage in both animals and patients (Dreier et al., 2009; Hartings et al., 2011b; Leão, 1947; Somjen, 2001). It moreover implicates prolonged extracellular accumulation of neurotransmitters, including glutamate (Fabricius et al., 1993) during anoxic SD, although the initial peak concentration of glutamate seems not significantly different between anoxic SD and SD in well-supplied tissue.

Despite these important mechanistic differences, Somjen (2001) listed a number of arguments suggesting that anoxic SD is not a separate entity but belongs to the SD continuum. Consistent with this view, when SD spreads from severely energy depleted to normal tissue in focal ischemia, it changes gradually, rather than abruptly, from a terminal to a short-lasting pattern (Dreier et al., 2013a). Along this propagation path, the following features of SD persist: the magnitude of the neuronal depolarization and the principal ion changes involved; the waveform of the negative DC shift; the changes in holding current and input resistance of patch-clamped neurons; the intrinsic optical signal; the spread in the tissue; the beading of dendrites; the cytotoxic edema; and the abrupt release of neurotransmitters (Aitken et al., 1998; Bahar et al., 2000; Dietz et al., 2008; Farkas et al., 2010; Jarvis et al., 2001; Jing et al., 1994; Murphy et al., 2008; Risher et al., 2009, 2010; Somjen, 2001). In addition, in well-supplied tissue, SD can gradually transform into anoxic SD by inverse neurovascular coupling (cf. below) (Dreier, 2011; Dreier et al., 1998). Moreover, anoxic SD is not necessarily terminal but fully reversible without any signs of cellular damage when oxidative substrate supply is reestablished before the so-called commitment point (Murphy et al., 2008; Nozari et al., 2010), defined as the time when neurons start dying during SD (Somjen, 2004). Furthermore, subthalamic gray matter of the adult brain neither generates SD in response to potassium (cf. above) nor does it generate anoxic SD, but it depolarizes only slowly under oxygen-glucose deprivation. This difference between subthalamic gray matter and upper brain centers could underlie the lower vulnerability of subthalamic gray matter to ischemia and may be the basis for the so called "vegetative state," a feared complication following global ischemia, characterized by selective survival of neurons in gray matter below the thalamic/hypothalamic boundary zone (Brisson et al., 2014). Analogously, the lower vulnerability of upper brain centers during the neonatal period compared to the postnatal period might be at least partially explained by the observation that upper brain centers support neither potassium-induced SD nor anoxic SD during the neonatal period in contrast to the postnatal one; the evolutionary benefit is likely that birth is the point in the life cycle with the highest statistical risk for hypoxia (Somjen, 2004). Lastly, apart from anoxia/ischemia, several conditions that do not compromise the partial pressure of oxygen can also cause long-lasting up to terminal SD; these include aglycemia, or presence of chemicals in the tissue like high potassium, veratridine, ouabain, palytoxin, etc. (Balestrino et al., 1999; Brisson et al., 2014; Dreier et al., 2013a). Among these conditions there are important differences in the mechanisms of initiation and recovery (Pietrobon and Moskowitz, 2014), but the phenomenology of SD remains remarkably stable. This suggests that mechanistically, there are not only differences but also overlaps. Anoxic SD and SD in naive tissue may thus be seen as two extremes of a continuous spectrum.

Neuronal Ion Conductances and SD Pharmacology

The abruptness of SD suggests explosive opening of cation conductances at its onset. Animal models of FHM1 and FHM3 suggest the involvement of voltage-gated cation channels. FHM1 results from mutations in the CACNA1A gene, encoding the pore-forming α1 subunit of neuronal voltage-gated Cav2.1 P/Q-type calcium channels (Joutel et al., 1993), and FHM3 from mutations in the SCN1A gene, encoding the α1 subunit of Nav1.1 voltage-gated sodium channels (Dichgans et al., 2005). Functional studies of both mutated channels indicated gain in function (Dichgans et al., 2005; van den Maagdenberg et al., 2004). Notably, the knockin mouse model for FHM1, which carries the human pure FHM1 R192Q mutation, displays increased propagation velocity and susceptibility to SD (van den Maagdenberg et al., 2004), resulting from enhanced glutamatergic transmission as functionally augmented P/Q-type calcium channels mediate presynaptic glutamate release by vesicular exocytosis (Tottene et al., 2009).

The channels that participate in initiation and spread of SD vary depending on tissue conditions. Specifically, NMDA receptor antagonists effectively abolish SDs in well supplied tissue (Marrannes et al., 1988), but are ineffective in severely ischemic or hypoxic tissue (Hernández-Cáceres et al., 1987; Müller and Somjen, 1998). Consistently, in the majority of patients with subarachnoid hemorrhage (SAH) and TBI, the NMDA receptor antagonist ketamine significantly inhibited SDs (Hertle et al., 2012; Sakowitz et al., 2009), but in a fraction of the patient population SDs were resistant to the same drug (Dreier et al., 2009). The gradual increase in baseline potassium before onset of anoxic SD (Figures 1C and 1D) is presumably among the factors rendering SD resistant to NMDA receptor antagonists under ischemia, because artificial rise in baseline potassium alone, i.e., in absence of ischemia, had the same effect in vivo and in brain slices (Petzold et al., 2005b). Another important influential factor might be the tissue acidosis before anoxic SD, as acidosis strongly inhibits NMDA receptor activation (Tong and Chesler, 2000). In focal ischemia, the penumbra is the transition zone between severely ischemic and adequately supplied tissue

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Box 2.

Pharmacology of SD is determined by processes that precede and trigger it. This partially explains the failure of clinical trials of NMDA receptor antagonists in stroke. In severely ischemic tissue, SDs are resistant to NMDA receptor antagonists, whereas in the penumbra they become increasingly pharmacosensitive as they move away from the ischemic center. Blocking SDs in the peripheral penumbra might have been beneficial in clinical trials, but this was possibly outweighed by their blockade in well perfused, surrounding tissue where they may precondition the tissue and promote regeneration and plasticity (Dreier, 2011). The oligemia following SD in surrounding tissue may reduce the steal-effect on rCBF in the ischemic zone (Figure 3C). Furthermore, SD activates microglia, thereby inducing expression of potentially beneficial cytokines (Jander et al., 2001). A caveat though is that at least part of the preconditioning effects attributed to SD could be a direct consequence of the lesion induced by local potassium application (Muramatsu et al., 2004).

(Hossmann, 1994). NMDA receptor antagonists consistently blocked SD in the peripheral penumbra. Only this part of the tissue showed improved survival (Eikermann-Haerter et al., 2012; Hartings et al., 2003; Iijima et al., 1992) (cf. Box 2 regarding NMDA receptor antagonist trials in stroke).

In hypoxic brain slices, only blockade of all major cation channels prevented anoxic SD. The drug cocktail that effectively prevented anoxic SD targeted voltage-gated sodium and calcium channels as well as NMDA and AMPA/kainate receptor-controlled channels (Müller and Somjen, 1998). In most studies, single channel blockers alone were insufficient for preventing anoxic SD; inhibitors of voltage-gated sodium channels, such as tetrodotoxin, lidocaine or dibucaine, were the single-channel blockers that produced the most significant delay from oxygen depletion to anoxic SD (Pietrobon and Moskowitz, 2014), even at concentrations that only partially inhibited evoked field potentials or axonal conduction (Risher et al., 2011). A smaller delay of anoxic SD was produced by inhibitors of voltage-gated calcium channels (Jing et al., 1993; Yamamoto et al., 1997).

The pharmacological profile of SDs under various tissue conditions, including exposure to hypoxia, potassium, ouabain, electric current, or trauma, was previously reviewed (Pietrobon and Moskowitz, 2014; Somjen, 2001). This incompletely understood profile is beyond the scope of this paper. It is important to note though, that the majority of tissue conditions that trigger SD in vivo are focal and are characterized by gradients of intensity or concentration of the trigger across the tissue. For example, in potassium-induced SD, there is a gradient of baseline potassium, on which SDs are superimposed (Petzold et al., 2005b); in focal ischemia, lack in oxygen and glucose show gradients as well. Speculatively, trigger-dependent mechanisms follow these spatial gradients in a dose-dependent manner, which would imply a seamless transition at the border zone between two neighboring tissue conditions, indicating not only differences but also shared mechanisms between the different wave sections (Figure 2). Consistently, trigger-dependent modifications of several aspects of SD phenomenology change gradually rather than abruptly when the wave propagates from one tissue condition to the next; this includes: DC shape and duration, depression pattern (cf. below), intrinsic optic signal, neurovascular response (cf. below) and propagation speed. Histopathological evidence further suggests that as one moves away from the center exposed to the trigger, the wave becomes less and less harmful. This is accompanied by faster recovery within the depolarization continuum, shifting the cell death mechanism toward apoptosis and, hence, to slower death within the necrotic-apoptotic continuum (Charriaut-Marlangue et al., 1996). This seamless transition also seems to apply to drug sensitivities. For instance, in experiments where the potassium threshold of SD was determined using stepwise rises of extracellular potassium, the sensitivity to NMDA receptor antagonists declined as a function of the baseline potassium concentration (Petzold et al., 2005b). Also, the upward shift in the electric stimulation threshold of SD by subsaturating doses of NMDA receptor antagonists fits into this picture (Marrannes et al., 1988).

The Role of Astrocytes

SD is primarily a disturbance of neurons. Astrocytes remain functional and support neuronal recovery. That neurons lead and astrocytes follow is exemplified by changes in intracellular calcium which rises first in neurons, then in astrocytes (Chuquet et al., 2007). Moreover, SD and the associated neuronal calcium wave remain unaffected when the astrocytic calcium wave is blocked by the depletion of internal calcium stores (Peters et al., 2003).

The protective role of astrocytes against SD is supported, for example, by an animal model of familial advanced sleep phase syndrome (FASPS) and migraine, a genetic disease of migraine with uncomplicated aura (Brennan et al., 2013). Specifically, a lower potassium threshold for SD was observed in mice engineered to carry the gene encoding casein kinase Iδ (CKIδ)-T44A allele, containing a missense mutation that co-segregated with the clinical syndrome in patients. Hypothetically, the mutation causes hypophosphorylation of connexin43 (Cx43), thereby reducing gap junctional communication. In another genetically modified mouse, astrocyte-directed inactivation of Cx43 reduced astrocytic gap junctional communication and was similarly associated with higher propensity to SD (Theis et al., 2003). Spatial potassium buffering requires functional gap junctions, which might explain their protective effect.

Moreover, astrocytic glycogen stores might play a protective role against SD. Thus, functional glycogenolysis in astrocytes decreased the propagation velocity of SD induced by either local microinjection of potassium chloride or oxygen-glucose deprivation and increased the latency from energy depletion to SD under oxygen-glucose deprivation (Allen et al., 2005; Seidel and Shuttleworth, 2011).

Under ischemia, the compensatory action of astrocytes is hindered because astrocytic Na,K-ATPases lack ATP. Then, intra-astrocytic sodium rises as observed in primary astrocyte culture under simulated ischemic conditions (Rose et al., 1998), and potassium is spilled out instead of taken up (Largo et al., 1996a). Correspondingly, in normoxic-normoglycemic tissue, astrocytes do not show large volume increases during SD, whereas they markedly swell during ischemia (Risher et al.,

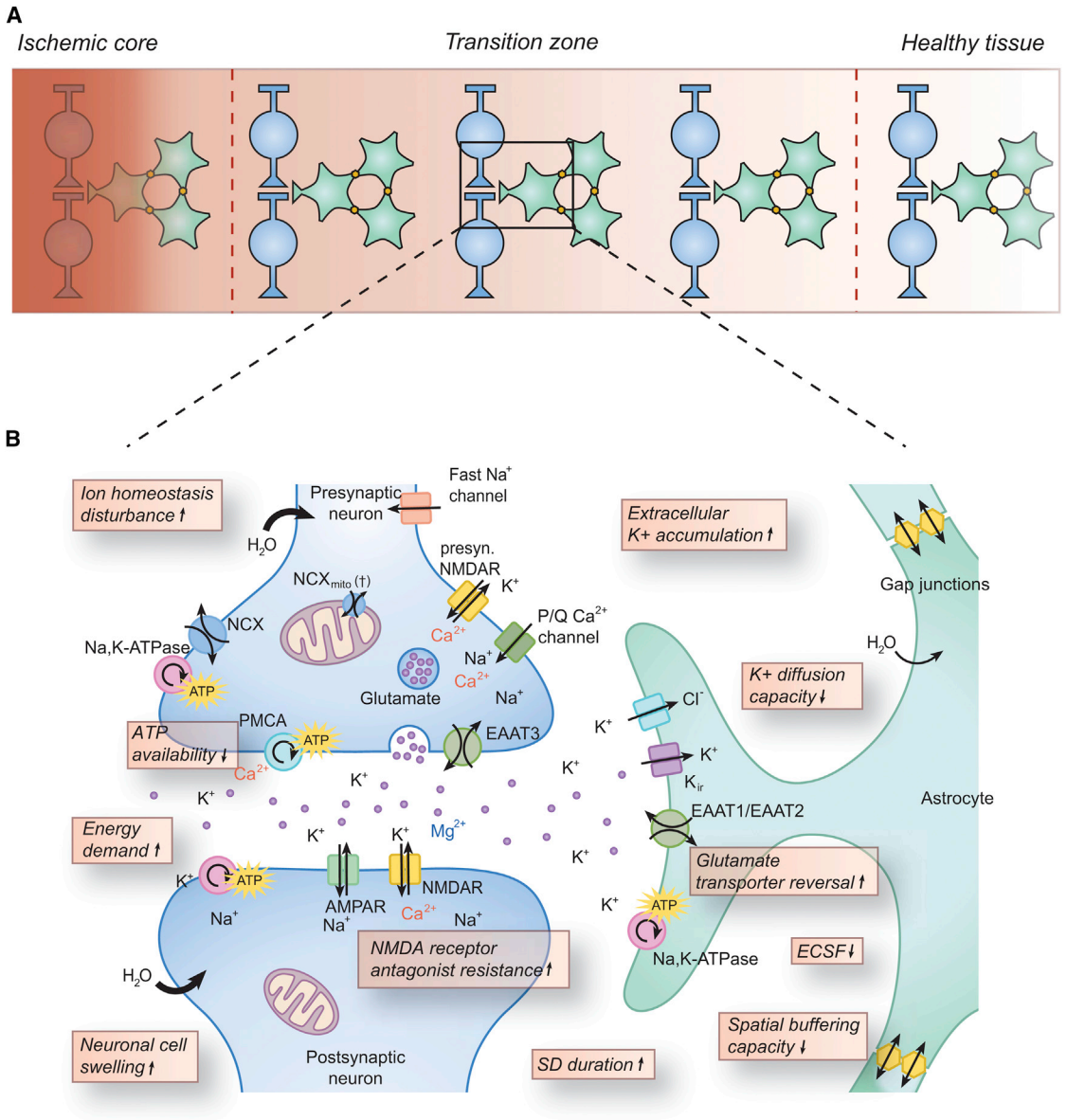

Figure 2. Gradually Changing Contribution of Cellular Mechanisms Involved in SD within the Transition Zone between Ischemic Center and Surrounding Well-Perfused Tissue

(A) Schematic of neuronal and astrocytic units. Brain cells are exposed to gradual decline of perfusion from right to left. In a reaction/diffusion type of process, SD runs rightward against the gradients of perfusion and oxidative substrates.

(B) Molecular and neurophysiological mechanisms involved in propagation and local persistence of SD differ between the ischemic core and the surrounding tissue. In the transition zone, these might blend with each other. The illustration depicts a tripartite glutamatergic synapse. Preeminently changing variables are highlighted using semitransparent boxes with the direction of change denoted by arrows in comparison to surrounding, well-nourished tissue. Emphasis has been placed on extracellular potassium accumulation and glutamatergic mechanisms.

K^+, potassium; Na^+, sodium; Ca^{2+}, calcium; Mg^{2+}, magnesium; Na,K-ATPase, sodium-potassium adenosine triphosphatase; PMCA, plasma membrane calcium ATPase; NCX, Na,Ca-antiport; NMDAR, N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; P/Q Ca^{2+} channel, P/Q type calcium channel; K_{ir}, inwardly rectifying potassium channel.

2009). Loss in astrocytic function may importantly limit neuronal survival under ischemia. In normoxic-normoglycemic tissue, even astrocytic failure alone was sufficient to induce SDs and, with delay, neuronal death (Largo et al., 1996b).

The so-called glucose paradox further underscores the importance of astrocytes (Schurr et al., 1999; Somjen, 2004): under experimental ischemia, hyperglycemia and acidosis delay the onset of SD, curtail it and promote recovery of synaptic transmission, whereas in the penumbra, low glucose levels further prolong SDs and increase their frequency (de Crespigny et al., 1999; Strong et al., 2000). Eventual cell death, however, was worse in hyperglycemic animals (Hansen, 1978; Kristián and

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Siesjö, 1998). This may stem from hyperglycemic augmentation of delayed death, presumably resulting from increased lactic acidosis which primarily injures astrocytes and causes their dissolution as they become significantly more acidotic than extracellular space or neurons under such conditions (Kraig and Chesler, 1990). A caveat though is that the dependence of ischemic cell death on serum glucose presumably describes a U-shaped curve. Clinical evidence that hypoglycemia can be fatal was found for example in an SAH case, in which iatrogenic insulin-triggered hypoglycemia resulted in a cluster of SDs with fatal outcome (Dreier et al., 2009). Cerebral microdialysis in patients with SAH correspondingly suggested that low cerebral glucose is associated with unfavorable outcome (Schlenk et al., 2008). SDs might play a causal role in this as they decreased dialysate glucose and increased dialysate lactate in experimental and clinical studies (Feuerstein et al., 2010).

Hemodynamic Responses to SD

In otherwise healthy cortex, the intense neuronal and astrocytic depolarization during SD acts as a potent stimulus to increase regional cerebral blood flow (rCBF) (= spreading hyperemia). The increased rCBF aims to meet the increased energy demand and to clear the extracellular space from metabolites (Figure 1A). A shallow initial hypoperfusion sometimes precedes the hyperemia, and a very prolonged, moderate hypoperfusion (= oligemia) follows it. This sequence of rCBF changes applies to naive cortex of almost all properly investigated mammals (Santos et al., 2014). With sufficient temporal resolution, traces of the blood-oxygen-level-dependent signal from a functional MRI study in migraineurs with aura suggest that the rCBF response to SD in otherwise healthy human cortex follows the same pattern (Hadjikhani et al., 2001). During oligemia, significant increase in the cerebral metabolic rate of oxygen ($CMRO_2$) was found (Piilgaard and Lauritzen, 2009). But, despite this and mild rCBF decrease, SD is not followed by histological damage in otherwise healthy cortex (Nedergaard and Hansen, 1988).

In contrast to SD's hemodynamic responses in healthy tissue, under pathological conditions SD can cause severe vasoconstriction instead of vasodilatation by inverse neurovascular coupling (Figure 1B) (Dreier, 2011; Dreier et al., 1998; Shin et al., 2006; Strong et al., 2007). This causes severe hypo- instead of hyperperfusion, which runs together with the depolarization wave in the tissue (= spreading ischemia). In contrast to the physiological oligemia (cf. above), spreading ischemia starts during the massive disturbance of ion homeostasis and delays its recovery. Hence, from a mechanistic perspective, spreading ischemia gradually shifts SD toward anoxic SD along the SD continuum. A key process underlying spreading ischemia is a vicious cycle between vasoconstrictors released by neurons/astrocytes and vasoconstriction-induced perpetuation of neuronal/astrocytic depolarization (Dreier, 2011). Interestingly, vasodilators such as the L-type calcium antagonist nimodipine or the NO-donor *S*-nitroso-*N*-acetylpenicillamine caused pharmacologically induced spreading ischemia to revert to almost normal spreading hyperemia (Dreier et al., 1998, 2001a).

When cortex tissue was selectively exposed to erythrocyte products in rats, spreading ischemias by themselves, i.e., without preceding ischemia, were sufficient to cause widespread cortical necrosis (Dreier et al., 2000). When spreading ischemias occurred as a consequence of middle cerebral artery occlusion (MCAO), they expanded the ischemic core (Shin et al., 2006; Strong et al., 2007). Spreading ischemia was also observed in rats during incomplete global forebrain ischemia (Bere et al., 2014). In pharmacological experiments, it resulted from NO synthase inhibition in combination with elevated baseline potassium (Dreier et al., 1998). A similar constellation could also be responsible for spreading ischemia after arterial occlusion as ischemia increases baseline potassium before the onset of SD (cf. above) and molecular oxygen is required for NO synthesis. In clinical studies, spreading ischemia was recorded in patients with SAH (Dreier et al., 2009), malignant hemispheric stroke (Woitzik et al., 2013), and TBI (Hinzman et al., 2014) with durations of more than 2 hr after SAH.

It might be added that the rCBF response to SD in naive cortex is different in mice, with relevance for the genetic models in this species. The mouse response starts with pronounced initial hypoperfusion, followed by a short peak that barely reaches baseline and renewed, very prolonged rCBF reduction by ~60% (Ayata et al., 2004). This is associated with a drop in $CMRO_2$. Concurrent severe hemoglobin desaturation suggests that oxygen metabolism becomes at least partially supply limited, and decrease in blood volume implies vasoconstriction as the mechanism (Yuzawa et al., 2012). Duration of the initial hypoperfusion correlates with duration of the negative DC shift, which could be interpreted as a slight push toward anoxic SD. Hence the hypoperfusion formally fulfills criteria for spreading ischemia (Dreier, 2011). The phenomenology of the whole response is nevertheless fundamentally different from spreading ischemia in rats, cats, or humans (Dreier et al., 1998, 2009; Strong et al., 2007). Interestingly, a rCBF response reminiscent of that in mice can be reproduced in rats through anesthesia with the vasodilator isoflurane (Feuerstein et al., 2014), which increases baseline rCBF by ~50% from the physiological level. The trough of the hypoemic response under isoflurane was not lower though than the oligemia under other anesthetic conditions; instead, it simply started from a higher level of flow. This may indicate that the physiological mouse response to SD is shifted toward higher vascular tone. This would explain tissue hypoxia in distant territories of mouse cortical capillaries during the trough (Takano et al., 2007). It should be noted though that the secondary, shallow negative DC shift during this phase is rather not a negative ultraslow potential (cf. below), as the concomitant extracellular potassium was not elevated (Chang et al., 2010).

Facilitation of Cell Death by SD in Metabolically Compromised Tissue

Experimental evidence that neuronal damage is facilitated by prolonged SD comes from MCAO models in which cumulative duration rather than sheer number of SDs correlated with infarct size (Dijkhuizen et al., 1999; Mies et al., 1993) and the dynamics of infarct growth (Hartings et al., 2003). Evidence that SD initiates neuronal death in metabolically compromised tissue stems from experiments in which SD was artificially triggered outside of a moderately hypoperfused zone and invaded it. Only when hypoperfused tissue was traversed by SD, histological sections demonstrated neuronal necrosis (Dreier et al., 2007).

The first SD erupts in the ischemic center ~2–5 min after MCAO. When tissue is reperfused in time, this initial

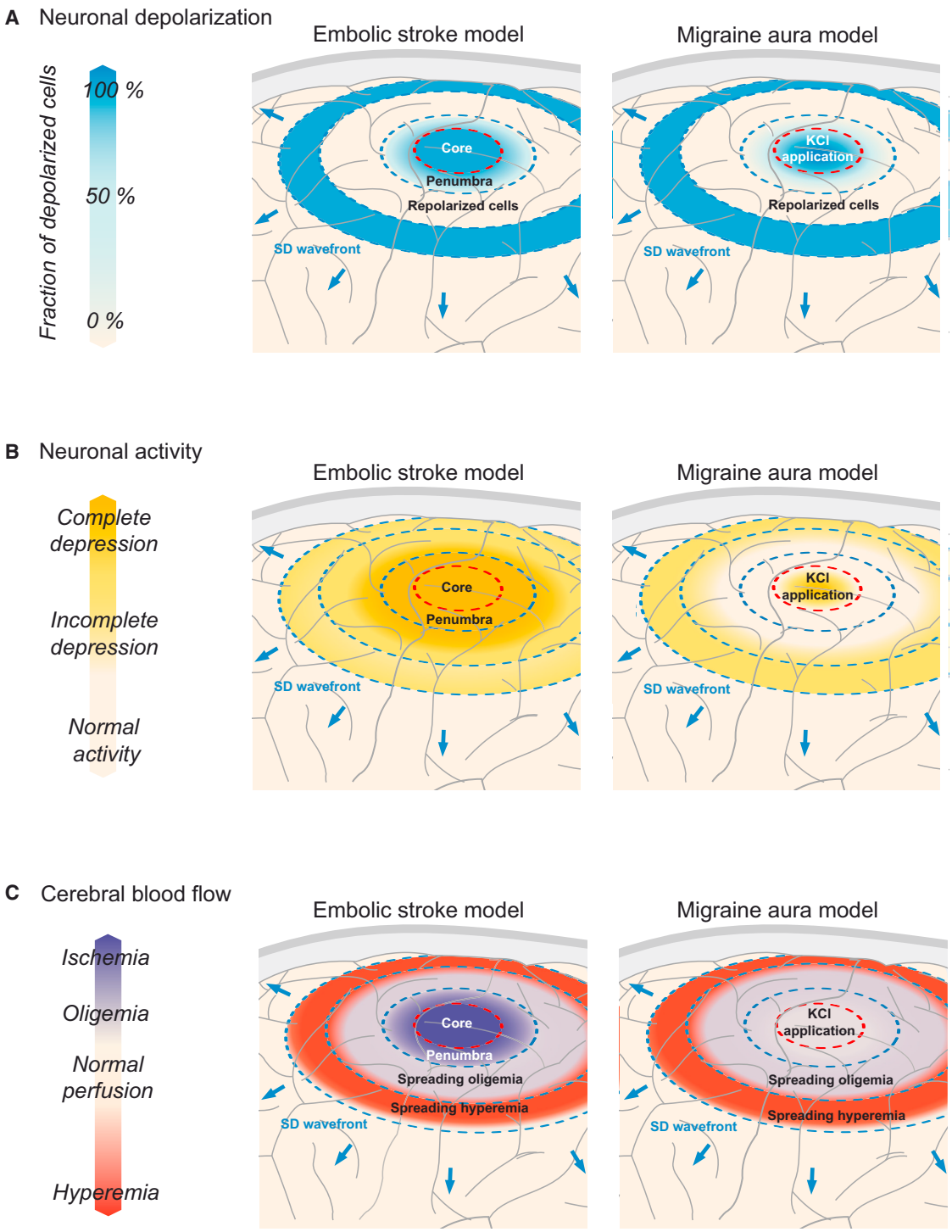

Figure 3. Snapshots of SD Triggered by Embolic Occlusion of a Cerebral Artery on the Left and by High Potassium on the Right

(A) In the embolic stroke model, the first SD starts in the ischemic center ~2–5 min after local circulatory arrest. In the experimental migraine aura model, the first SD starts at the application site of high potassium. In both models, the center region remains persistently depolarized thereafter. From the center, the SD runs into the normal, surrounding tissue. The snapshot shows a time point at which the SD front has already reached normal, surrounding tissue.

(B) In the embolic stroke model, the zone of persistent depression of activity extends into the normally perfused cortex surrounding the ischemic zone (Oliveira-Ferreira et al., 2010). In the high potassium model, persistent depression is observed at the potassium application site. In both models, spreading depression of activity will only be short-lasting far away from the trigger.

(legend continued on next page)

depolarization is fully reversible. SD sensu stricto hence only includes the initial depolarization until the commitment point (cf. above). When the depolarized state outlasts this point, the DC potential increasingly reflects cellular death. This late DC negativity is the negative ultraslow potential (Dreier et al., 2013a). After the first SD that originates in the ischemic center and concentrically invades the penumbra and surrounding tissue, subsequent SDs are generated at the rim of the permanently depolarized core (Dijkhuizen et al., 1999; Hossmann, 1994). They may spread locally only, or alternatively cycle around the depolarized core (Nakamura et al., 2010; Woitzik et al., 2013).

Even when SDs are not terminal, they can be followed by cell death if superimposed on a shallow negative ultraslow potential. For example, specific aconitase blockers, which selectively inhibit astrocyte oxidative metabolism, did not induce terminal depolarization but triggered a cluster of mildly prolonged SDs on a shallow negative ultraslow potential (Largo et al., 1996b). Similarly, recurrent, slightly prolonged SDs on a shallow negative ultraslow potential led to neuronal death in ET-1-exposed cortex (Oliveira-Ferreira et al., 2010). Notably, the negative ultraslow potential is accompanied by tissue acidosis and incomplete recovery of the other ion changes (Dreier et al., 2002; Largo et al., 1996b; Oliveira-Ferreira et al., 2010; Windmüller et al., 2005). If rCBF responses to SD are hyperemic, they may cause atypical transient alkaline shifts instead of the usual acidosis, indicating transient recovery from tissue lactic acidosis (Oliveira-Ferreira et al., 2010).

The pattern of mildly prolonged SDs on a shallow negative ultraslow potential seems important, as clinical pilot studies suggest that this pattern, rather than "classic" terminal depolarization, is predominantly measured in patients who develop new brain infarcts (Drenckhahn et al., 2012). Such clusters can recur after a quiescent period of several hours. After MCAO in rats, this led to further infarct growth (Hartings et al., 2003). Evidence for secondary clusters was also found in patients with malignant hemispheric stroke (Dohmen et al., 2008). It should be noted though that the term "SD cluster" is not yet well-defined in patients (Dreier et al., 2006). Current working definition for a clustered SD is that it occurs within 2 hr from the previous one (Sakowitz et al., 2013).

The Known Experimental Triggers of SD Are Either Potentially or Unequivocally Injurious

To our knowledge, brief ischemia in mice by injection of air microemboli into the carotid circulation, has been the only properly investigated experimental trigger so far, which was convincingly found to induce SD before the intensity or time of exposure reached the threshold for the induction of permanent neuronal damage in thorough histopathological analysis (Nozari et al., 2010). In other words, SD was triggered but no damage was found in the trigger zone.

Potassium is another important trigger of SD. The potassium threshold for SD in neocortical slices is between ~12 mM in young and ~16 mM in older animals (Maslarova et al., 2011). The threshold seems to be in a similar range in neocortex in vivo (Petzold et al., 2005b), but due to glial buffering, the potassium gradient between artificial cerebrospinal fluid (ACSF) and cortex is steep when potassium is applied topically to the brain. Thus, the ACSF potassium threshold was 56 mM in rats under barbiturate-anesthesia (Dreier et al., 2000; Petzold et al., 2008). Analogous to brief ischemia, potassium might trigger SD before it induces permanent neuronal damage in the trigger zone. But, this has not been properly investigated to our knowledge. A brief cluster of SDs, triggered by potassium slightly above threshold, resulted in minor signs of injury at the trigger site (scattered shrunken non-scalloped neurons with pericellular edema and a few TUNEL-positive cells). This injury increased further dependent on concentration, exposure time, and level of perfusion (Dreier et al., 2000, 2013b). Prolonged placement of a cotton ball soaked with 1 or 2 M potassium chloride on the pial surface is inevitably associated with small necrosis (Muramatsu et al., 2004).

Electric stimulation is often claimed to be non-injurious. However, electric stimulation for SD induction is of several magnitudes more intense than any pathological brain activity. No permanent neuronal damage may ensue in the trigger zone at the electric threshold but this has not been properly investigated to our knowledge. We previously found a small necrosis in rats when three SDs were triggered with stimulus intensity somewhat above threshold. Interestingly, consistent with a trauma-related mechanism, electrically triggered SD (Sugaya et al., 1975) seems to share the sensitivity to tetrodotoxin with trauma-triggered SD (Akerman et al., 2008) in contrast to SD triggered by a potassium chloride crystal (Sugaya et al., 1975) or high potassium dialysis (Herreras and Somjen, 1993b).

Thus, among the known experimental triggers of SD most are injurious, and no unequivocally non-injurious trigger has been convincingly identified so far. Nonetheless, non-injurious triggers might exist as propagation of SD can be seen as a process that triggers SD in neighboring tissue and SD is not associated with damage in naive tissue (Nedergaard and Hansen, 1988). Moreover, migraine aura is almost always a harmless clinical condition, which implies non-injurious triggers of SD.

Overlaps between Models of Migraine Aura, Stroke, and Epileptic Hyperexcitability

In view of the potentially injurious nature of the experimental triggers, an elegant illustration of the overlaps between models of migraine aura and stroke comes from considering animal models of SD in view of each of Leão's hypotheses. If the model of SD is investigated on the basis of Leão's SD hypothesis of migraine aura (Leão and Morison, 1945), not only the peripheral part of the wave but also the central part, where the experimental trigger is applied, is of interest. Vice versa, if the model is investigated on the basis of Leão's SD hypothesis of stroke (Leão, 1947), not only the central part but also the peripheral part in the adequately supplied tissue should be considered, otherwise risking a selective analysis bias (Figure 3). Overlaps between models of migraine aura and stroke are also illustrated by comparing high

(C) Only in the embolic stroke model, an ischemic zone is observed.
If shortly after the situation illustrated by the snapshots the embolus is resolved or the potassium disappears, cells will repolarize and no damage will develop. Otherwise, neurons will die; in the potassium model however this process will take longer because the perfusion deficit accelerates cell death during SD (Dreier et al., 2013b).

potassium and ET-1 model of SD (Dreier et al., 2002) or models of cerebral microembolism with relevance for migraine with aura in patients with cardiac/extracardiac right-to-left shunts (Nozari et al., 2010). More complex overlaps were furthermore identified in genetically engineered mice carrying FHM1 Cav2.1 mutations, which showed increased vulnerability to MCAO (Eikermann-Haerter et al., 2012).

One hypothesis regarding SD in patients with migraine aura is that SD in these patients emerges from episodic disruptions of the excitation-inhibition balance and hyperactivity of cortical circuits due to excessive recurrent excitation (Tottene et al., 2009). It would be important to study, in animal models of increased propensity to SD, whether physiological models of functional activation trigger SD based on the above mentioned hypothesis. To take this hypothesis further, it would also be helpful if animal models were identified in which isolated SDs spontaneously developed in otherwise healthy cortex, analogous to animal models of spontaneous IEEs. To some degree, hyperexcitability underlying spontaneous SDs might in fact share mechanisms with acute epileptic hyperexcitability, as (1) SDs are often encountered in models of acute status epilepticus (Avoli et al., 1991), (2) SDs and IEEs co-occur in patients with acute cerebral injuries such as stroke or TBI (Dreier et al., 2012; Fabricius et al., 2008), and (3) genetic predispositions to epilepsy and migraine aura overlap (Winawer and Connors, 2013). For example, mutation carriers for all three genes associated with FHM were reported who also developed epileptic seizures (Costa et al., 2014).

Interestingly, similarly to the kindling of chronic IEEs by artificially triggered IEEs, a recent clinical study on post-injury epilepsy in patients with SAH suggested that repeated SDs could kindle chronic IEEs (Dreier et al., 2012). By contrast, both repeated IEEs and SDs seem to have inhibiting or "anti-kindling" effects on SD; supporting evidence includes the following: (1) in various models, the susceptibility to SD decreased during epileptogenesis (Köhling et al., 2003; Koroleva et al., 1993; Maslarova et al., 2011; Tomkins et al., 2007), (2) SDs do not invade penicillin-induced epileptic foci but typically circulate around them (Koroleva and Bures, 1979), (3) single daily SDs induced for 1 or 2 weeks in mice decreased the susceptibility to SD (Sukhotinsky et al., 2011), and (4) even within the same cluster of SDs, subsequent SDs typically propagate through a smaller region than the first SD (James et al., 1999). In the light of these observations, it appears that there are strikingly different types of pathologic hyperexcitability states in the brain which can be associated with either increased or decreased susceptibility to SD.

Part II: Clinical Pictures in the Context of SD

Spreading Depression of Activity

Spreading depression of spontaneous activity is observed in the ECoG as silence in frequencies above ~0.5 Hz, running between different electrodes (Dreier et al., 2006; Fabricius et al., 2006; Leão, 1944) (cf. HF-ECoG in Figure 1A and 1B). SD seems to initiate spreading depression because the sustained depolarization exceeds the inactivation threshold for the action potential generating channels (Kager et al., 2002). The depression nevertheless outlasts the depolarization, suggesting that it is maintained by other mechanisms such as intracellular zinc, calcium, and/or adenosine accumulation (Carter et al., 2013; Lindquist and Shuttleworth, 2012). A new SD can start before the depression caused by the preceding SD has finished (Dohmen et al., 2008; Dreier et al., 2006; Fabricius et al., 2006). The DC shift of this new SD is often identical to that of the preceding SD. Such a constellation however indicates shortage of energy unless it results from a sedative. In a prospective, observational multicenter trial of 103 patients with TBI, such SDs in isoelectric tissue (= isoelectric SD) in contrast to SDs in electrically active tissue were associated with a highly significant 8-fold increase in the risk of unfavorable outcome at 6 months (Hartings et al., 2011a). When this category was added as a covariate to a regression model that included a prognostic score based on variables at admission, it increased the proportion of variance in clinical outcome from 9% to 22% that could be attributed to predictors.

The duration of depression thus serves as another summary measure for the tissue energy status in addition to the negative DC shift duration (Dreier et al., 2006; Fabricius et al., 2006). Notably, in experimental focal ischemia, the zone of persistent depression between recurrent SDs, in contrast to the zone with prolonged negative DC shifts, extends into the normally perfused cortex surrounding the ischemic zone (Oliveira-Ferreira et al., 2010). The negative DC shift duration is thus a more precise local biomarker for the energy status than the depression duration, but prolonged depression can be used as a biomarker to detect a new ischemic event when recording electrodes are positioned outside of the actual ischemic zone. This has relevance for clinical monitoring in patients at risk for delayed cerebral ischemia after SAH or secondary deterioration after TBI (Hartings et al., 2011b; Oliveira-Ferreira et al., 2010).

Nonspreading Depression of Activity

Nonspreading depression of spontaneous activity was originally described by Leão (1947) based on rabbit experiments of global cerebral ischemia. In the electroencephalogram (EEG), the first signs of nonspreading depression start within seconds of circulatory arrest with an arousal reaction of fast, irregular low-voltage activity. Isoelectricity is reached within 30–40 s, well before the neuronal ATP pool is depleted. As opposed to spreading depression, nonspreading depression does not run between different brain regions but develops simultaneously in the whole area exposed to oxygen depletion (cf. HF-ECoG in Figures 1C and 1D).

The subtle initial EEG changes of nonspreading depression are already associated with a profound neurological deficit, as it only takes 7 s from circulatory arrest until normal individuals lose consciousness. The perfusion threshold for complete, i.e., isoelectric, nonspreading depression ranges between 15 and 23 ml/100 g/min (Hossmann, 1994).

Without timely reperfusion, SD erupts in the ischemic center not earlier than ~1–4 min after onset of nonspreading depression, and SD rather than nonspreading depression initiates the cascades that eventually lead to cell death (Dreier, 2011; Leão, 1947). SD may start either at multiple foci (Jarvis et al., 2001) or at only one focus (Farkas et al., 2010). Evidently, SD cannot initiate spreading depression in the isoelectric tissue as there is no activity that could be depressed. This changes, in focal

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ischemia, when SD invades tissue further away, where nonspreading depression is less complete. The further away from the ischemic center, the more SD hence causes spreading depression.

How hypoxic neurons and astrocytes sense diminishing oxygen levels is unknown. But several local mechanisms were proposed as mediating the depression, including (1) alterations in vesicular transmitter release (Fleidervish et al., 2001), (2) activation of ATP-sensitive or G protein–dependent calcium-sensitive potassium channels (Erdemli et al., 1998; Müller and Somjen, 2000a), (3) release of adenosine by astrocytes (Canals et al., 2008), (4) acidosis, and (5) breakdown of gamma oscillations ("interneuron energy hypothesis") (Kann et al., 2014). Notably, nonspreading depression is associated with neuronal hyperpolarization, in stark contrast to the depolarization block that underlies spreading depression (Müller and Somjen, 2000a; Tanaka et al., 1997).

Nonspreading depression is presumably an "austerity program" to curb neuronal energy usage by the shutdown of nonessential cell functions well before prospects of tissue recovery vanish (Hochachka et al., 1996). This strategy might be highly effective, as about three quarters of brain energy are consumed by neural computation. Importantly, all this implies that nonspreading depression and SD are entirely different phenomena.

The Clinical Correlates of Sustained Depolarizations

History, examination, and clinical judgment remain the pillars of diagnosis and treatment even in the era of modern technology, although technology can obviously be used to support clinical decision-making. Problems arise when observations obtained with new technologies contradict well-established clinical concepts. These concepts, then, need to be revised. Observation of SDs with modern technologies in migraine aura and stroke is among the most prominent examples of such dilemmas, as patient percepts and clinical courses could hardly be more different between the two diseases, and at first glance, it seems impossible to relate them to a common pathophenomenological basis. This forms a major obstacle to a complete concept of the SD-diseases and will therefore be addressed in detail in the following.

No matter which body system the neurologist examines, without technological aids, only repercussions of changes in brain activity on body functions can be evaluated, but the pathological processes which cause the changes in activity cannot be directly observed. To put it figuratively, history and examination only inform the neurologist about the shadows that pathological processes cast over body functions through their effects on brain activity. The nature of these shadows builds the basis of the neurologist's clinical approach. The neurologist thus faces a fundamental philosophical problem, analogous to Plato's cave allegory as further explained in Figure 4. In translating Plato's cave allegory to neurology, understanding the pathological process underlying an epileptic seizure might be comparatively simple because, rather than casting a shadow over brain activity and body function, the pathological process, namely an IEE, is associated with a characteristic excess in brain activity that drives an excess in body function such as stiffness of limbs followed by jerking movements during a tonic-clonic seizure. The neurologist can see this with his own eyes. When technological aids such as electrographic recordings then "liberate" him from the "cave," he might quickly grasp the connection between excess in body function and the "real object," the IEE. The correspondence between abnormal brain function and change in body function was in fact so obvious that, in 1870, based on clinical observation and judgment alone and long before the EEG was invented by Hans Berger in 1924, John Hughlings Jackson came up with the hypothesis that an epileptic seizure arises from an occasional, excessive, and disorderly discharge of gray matter.

In contrast to an epileptic seizure, migraine aura represents a condition corresponding to a shadow on the proverbial cave's wall (cf. HF-ECoG in Figures 1A and 4A). This shadow can be directly seen by the patient and described to his neurologist. Accordingly, the neuropsychologist Karl Lashley referred to this shadow as a "scotoma" (= "darkness" in ancient Greek) (Lashley, 1941). Often surrounded by a narrow scintillating rim, this slowly growing, kidney-shaped shadow usually starts in the visual field center, running to the periphery within ~10–15 min. Lashley hypothesized that the underlying process, the "real object," corresponds to a wave of intense excitation in the primary visual cortex, creeping forward at a velocity of 3 mm/min, followed by a longer period of inhibition. The scintillating rim is presumably produced by synchronization of initial firing among nearby neurons, termed epileptoid activity, which locally lasts for ~1–5 s and presents as a high-frequency burst of population spikes (Herreras et al., 1994). Rather than inhibition, however, a depolarization block is responsible for the decline in spontaneous activity. Aristides Leão was the first to observe this when he electrically triggered spreading depression of spontaneous activity in the rabbit cortex (Leão, 1944). In 1945, he speculated that this is the pathophysiological correlate of the migraine aura (Leão and Morison, 1945). In 1947, he discovered the underlying process casting the shadow over the activity, when he observed the large negative DC shift of SD and correctly hypothesized that it reflects pronounced depolarization of neurons (Canals et al., 2005; Leão, 1947).

In the field of migraine aura, "liberation" from the "cave" has required a longer march than in epileptology, and electrographic evidence of SD during migraine aura is still missing. However, imaging studies of changes in rCBF or its surrogates during migraine aura strongly supported Leão's hypothesis (Hadjikhani et al., 2001; Olesen et al., 1981). Consistent evidence was also provided by magnetoencephalography (Bowyer et al., 2001). Nevertheless, it was claimed for decades that Leão's hypothesis is invalid because SDs would not occur in the human brain, based on unsuccessful attempts to trigger them in chronically epileptic patients and a seeming lack of SD correlates in the scalp EEG. Only in the last two decades, subdural ECoG recordings in patients and measurements in brain slices provided unequivocal electrophysiological evidence that SDs do occur in the human brain (Avoli et al., 1991; Dohmen et al., 2008; Dreier et al., 2006, 2009; Fabricius et al., 2006; Hartings et al., 2011a, 2011b; Mayevsky et al., 1996; Strong et al., 2002). SD's correlates in the scalp EEG were identified with simultaneous recordings of subdural ECoG and continuous scalp EEG (cEEG) (Drenckhahn et al., 2012; Hartings et al., 2014), and animal studies revealed that the propensity to SD markedly declines in

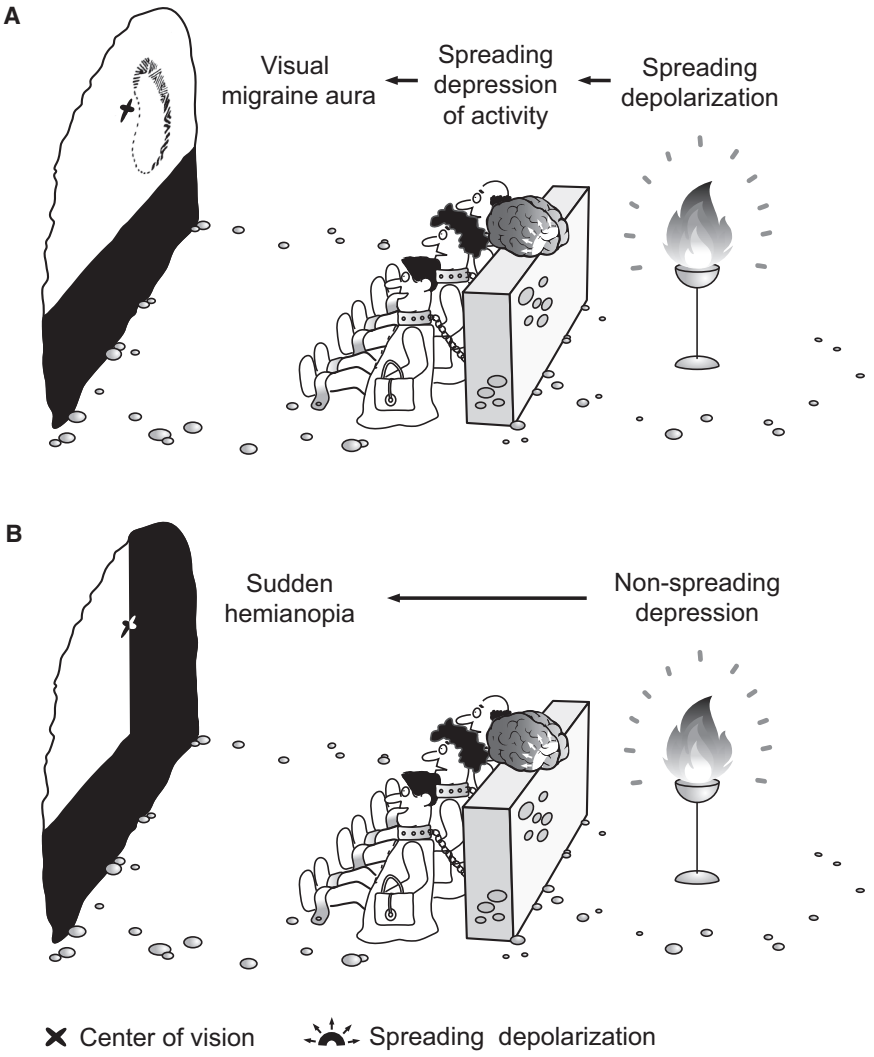

Figure 4. A Visual Migraine Aura and a Sudden Hemianopia as Two Different Shadows in Plato's Allegory of the Cave

When a neurologist investigates the visual system, only the repercussions of changes in brain activity on the patient's vision can be evaluated, while the pathological processes causing these changes cannot be directly observed. Thus, the neurologist is only informed about "shadows" that pathological processes cast over the patient's vision through their effects on brain activity. In his allegory of the cave, Plato had Socrates investigate a fundamental philosophical problem that relates to this neurological conundrum. In his fable, prisoners have lived enchained in a cave all of their lives, facing a blank wall. Objects are passing in front of a fire behind them, casting shadows on the wall. Socrates depicts this scene to Glaucon, explaining that the shadows are as close as the prisoners get to viewing reality. He describes the prisoners' reaction when they are freed and asks whether the prisoners will not fancy at first that the shadows that they formerly watched are truer than the real objects they now see, concluding that the philosopher is like a prisoner who is liberated and slowly comes to understand that the shadows do not make up reality, as he can perceive real objects rather than the mere shadows seen by the prisoners. Notably, the level of difficulty in linking a specific shadow to its corresponding real object depends on the object's form and position relative to the fire.

(A) In the cartoon, the shadow on the cave's wall is a migraine aura in the right visual hemifield of a patient. By contrast, the "real object" is an SD that runs in the fully electrically active, contralateral, primary visual cortex where it locally causes spreading depression of neuronal activity.

(B) Obviously, the allegorical prisoner would be unable to link a shadow to its actual object when the object is masked by another object in between. This is the case in ischemic stroke, which occurs in the left posterior cerebral artery territory in this example. Within seconds of rCBF decline, nonspreading depression of brain activity will cause sudden, right-sided hemianopia. When SD then erupts in the ischemic zone ~1–4 min later, it escapes attention of the patient, and thus the neurologist, either because it is not associated at all with spreading depression, or because the remaining activity is already so disturbed that further depression will not entail a patient percept. Thus, SD reveals itself to the neurologist during migraine attacks, when it is relatively harmless, whereas ironically, when potentially deleterious such as in stroke, it runs through the tissue unobserved under the "shadow" of nonspreading depression of activity.

the course of epileptogenesis (Köhling et al., 2003; Koroleva et al., 1993; Maslarova et al., 2011; Tomkins et al., 2007).

As mentioned, the fundamental electrographic evidence for SDs has not been found in patients with migraine aura; it has been found though in patients with stroke and TBI, and this brings us to the third shadow on the proverbial cave's wall. Different from that of migraine aura, this shadow does not grow slowly in one visual hemifield, but instead, the patient perceives the disappearance of a whole hemifield at once, or even the simultaneous disappearance of several modalities at once, such as a loss of movement in the right arm together with a loss of language. This type of sudden neurological deficit, which affects different cortical representation fields simultaneously, characterizes the shadow typical of stroke and might be produced by nonspreading depression of activity (cf. HF-ECoG in Figures 1C, 1D, and 4B). When SD then erupts in the ischemic zone ~1–4 min later (Leão, 1947), it might escape the patient's and clinician's attention either because it is not associated with spreading depression at all, or because the remaining activity is already so disturbed that further depression does not entail a neuropsychological correlate.

If so, one could say that SD presents itself to the clinician only during migraine attacks when it is relatively harmless, but it runs regularly across the tissue non-detected, under the shadow of nonspreading depression of activity, when it is potentially deleterious as in stroke. This insidious nature has led to the popular clinical misconception that SD is harmless in the human brain. It might be added that the analysis of the relationship between the "real objects," i.e., the depression and depolarization patterns in the ECoG, and the patients' percepts, is just at its infancy. So far, the most important preliminary findings are that conscious and oriented patients with subdural recording strips

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do not usually describe any obvious percept when a single SD is running on the monitor, although the majority of these single SDs are associated with spreading depression. Clusters of recurrent isoelectric SDs were associated with new transient or permanent neurological deficits such as a state of mutism or a hemiparesis, but the patients did not report symptoms typical of migraine aura (Dreier et al., 2006). One patient, who had suffered aneurysmal SAH and was initially awake, displayed a waxing and waning delayed ischemic neurological deficit synchronously to a waxing and waning of SD clusters on the monitor. Following the clusters, the activity always recovered until a prolonged cluster was finally associated with (1) a permanent deficit, (2) no recovery of activity, and (3) a new infarct on neuroimaging. Although further systematic neuropsychological studies are necessary to investigate these issues, it should be stressed that the clinical evidence from conscious patients with stroke or TBI, who did not undergo SD monitoring, is already overwhelming that migraine aura is very rare in these patients, whereas, when the patients are properly monitored, it is not unusual to witness SDs.

Migraine Aura and Cerebrovascular Disease

Based on the vascular hypothesis of migraine by Harold Wolff, numerous articles on migraine between 1960 and 1980 started with openings along the lines of: "It is widely accepted that the aura arises from intracranial vasospasm and headache from extracranial vasodilatation" (Blau, 2004). However, it is well established now that extracranial vasodilatation is neither necessary nor sufficient for migraine headache (Charles and Baca, 2013; Pietrobon and Moskowitz, 2014). A different question is whether the SD hypothesis of migraine aura implies that the aura cannot arise from intracranial vasospasm. The answer is that Leão's hypothesis does not exclude Wolff's hypothesis of the aura, as, for example, intracranial vasoconstriction by ET-1 potently triggers SD in rodents in vivo (Dreier et al., 2002, 2007). Whether or not a patient will perceive migraine aura will be determined by the following, rather than by the vascular/non-vascular nature of the trigger: (1) will the SD not only run through ischemic tissue, but also through a perceptual and eloquent brain region, which is not ischemic and thus not subject to nonspreading depression of activity before arrival of the wave; and (2) is the patient not only conscious but self-aware enough to be able to perceive and report the aura symptoms. That there are also vascular triggers to migraine aura is suggested by the following: Migraine aura can be ignited by cerebral angiography, cardioembolic conditions, extracranial cervicocephalic artery dissection (D'Anglejan-Chatillon et al., 1989; Nozari et al., 2010) or acute aneurysmal SAH (Dreier et al., 2001b). In the rCBF studies using intracarotid ^{133}Xe, the large number of recorded migraine auras resulted from the procedure of catheterizing and injecting the carotid artery, which provoked visual aura in more than 50% of migraineurs (Lassen and Friberg, 1991). In rare cases, a status aurae migrainalis can be induced by severe stenosis of the internal carotid artery (Olesen et al., 1993), which seems to respond to carotid thromboendarterectomy (Klingebiel et al., 2008). Further associations between migraine aura and cerebrovascular disease were found in several Mendelian variants of small vessel disease such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS), and mutations in the COL4A1-gene (Dichgans et al., 1998; Lanfranconi and Markus, 2010). Moreover, transient global amnesia is interesting, as studies found an association with migraine, and MRI typically shows a transient, dot-like diffusion anomaly in hippocampal area CA1, a very sensitive area to metabolic and oxidative stress (Bartsch et al., 2010). Furthermore, all recent hospital- and population-based epidemiological studies demonstrated a slightly but significantly increased risk for ischemic stroke in people who have migraine with aura, contrasting with migraine without aura (Kurth et al., 2012). It might be added that true migrainous stroke, as defined by the International Headache Society (Figure 1B), is much too rare to explain this epidemiological association.

In neuroimaging studies, a fraction of migraineurs displayed white matter anomalies, consistent with small vessel disease (Kurth et al., 2012). These are unlikely due to SDs, as SDs are restricted to gray matter. However, the underlying small vessel disease may not only lead to damage to white matter tracts but also to cortical microinfarcts, sufficient to trigger SD but too small to be detected by 1.5 or 3 T MRI, as suggested by an animal study using 9.4 T MRI (Nozari et al., 2010) and by a recent clinical study on cortical microinfarcts using 7 T MRI (van Veluw et al., 2013). Hypothetically, such cortical microinfarcts could contribute to cortical atrophy in severe forms of migraine aura-linked small vessel disease such as CADASIL.

Lastly and importantly, not all the very rare cases of migraine aura with devastating clinical outcome are related to ischemia. For example, FHM can show the life-threatening condition of fever, coma, focal signs, and delayed hemispheric cortical swelling. With rare exceptions, this delayed cortical edema is not cytotoxic but vasogenic (Butteriss et al., 2003; Dreier et al., 2005) and may result from SD-induced BBB disruption via matrix metalloproteinase-9 activation (Gursoy-Ozdemir et al., 2004).

This plethora of observations suggests that the SD hypothesis can gather an enormous bandwidth of partially harmless, partially deleterious clinical conditions under one roof. Rather than fundamentally different phenomena, relatively subtle mechanistic differences within the SD continuum in time and space, in concert with overlaps of other processes that change neuronal activity, are sufficient to explain largely different clinical manifestations. Another aspect of this framework is that pathways leading to very similar clinical manifestations may originate from either initial disruptions of the neural system followed by vascular system disruption, or the other way around, with the vascular system leading. In fact, it seems a hallmark of the whole class of SD-related neurological disorders that vascular and non-vascular mechanisms are often inextricably linked (Brennan and Charles, 2010; Dreier, 2011).

SD and Headache

Migraine occurs in ~18% of women and 6% of men, with the cross-study rate of migraine with aura being 4.4% (Merikangas, 2013). The aura typically precedes the headache and could hence be the trigger for it. SD, in fact, releases a plethora of molecules into the extracellular space including proinflammatory factors such as potassium, protons, arachidonic acid, serotonin, and NO (Gold et al., 1998; Hansen and Zeuthen, 1981; Lauritzen et al., 1990; Mutch and Hansen, 1984; Petzold et al., 2008). Experimental evidence suggests that this is sufficient to activate

and sensitize meningeal afferents, to discharge trigeminal axons and to activate second-order neurons which could mediate the headache (Pietrobon and Moskowitz, 2013). In a complementary fashion, parenchymal inflammation and trigeminovascular activation may result from SD-induced opening of pannexin-1 hemichannels and caspase-1 activation (Karatas et al., 2013).

Notably, migraine headache can be triggered by intravenous nitroglycerin after conversion to NO (Schytz et al., 2010). In rats, NO correspondingly induces delayed dural inflammation (Reuter et al., 2001). SD, however, does not cause this dural inflammation as NO does not trigger SD. Decreased rather than increased NO enhanced the susceptibility to SD in vivo and in vitro in rodents (Petzold et al., 2005a, 2008), and NO consistently reduced the propagation velocity of SD in the chicken retina (Ulmer et al., 1995). Accordingly, nitroglycerin did not provoke migraine aura in patients (Afridi et al., 2004). Of note, NO triggers migraine headache in migraineurs (with and without aura), but does not trigger (1) SD in animals, (2) migraine aura in patients, and (3) migraine headache in healthy subjects. Collectively, these observations strongly suggest that migraineurs carry a special propensity to trigeminovascular pain which is independent of SD. This propensity might be the prerequisite for triggers such as SD or NO to trigger migraine headache. Consistently, SD per se is not an aversive stimulus in awake animals (Charles and Baca, 2013; Koroleva and Bures, 1993; Pietrobon and Moskowitz, 2013).

Further evidence for the argument that SD cannot trigger headache without propensity to trigeminovascular pain comes from the symptom of visual migraine auras without headache. In the Framingham cohort, visual migraine auras were thus reported by 1.23% of subjects (Wijman et al., 1998). In 77% of the affected subjects these auras started after the age of 50; in 58% they were never accompanied by headaches; and 42% of subjects had no headache history. Migraine headache typically decreases with advancing age. In patients in whom isolated auras start after the age of 50, lack of migraine headache may hence indicate trigeminovascular changes with aging. In younger patients, the propensity to trigeminovascular pain must be absent for other reasons.

With regards to headache in the context of stroke, ischemic stroke patients report headache at stroke onset in only one-quarter of cases (Tentschert et al., 2005). Among these with headache at stroke onset, only one-quarter fulfilled the ICHD-II criteria for migraine headache. This makes a simple cause-effect relationship between SD and migraine headache further unlikely as a migraine aura is produced by only one SD but (consistent with animal recordings) human recordings in ischemic stroke displayed dozens up to over 200 SDs in practically all subjects with electrodes over viable tissue (Dohmen et al., 2008). SD may nevertheless trigger migraine headache when the stroke coincides with the postulated propensity to trigeminovascular pain. Consistently, in multivariate analysis, headache at stroke onset was significantly associated with a history of migraine headache (Tentschert et al., 2005). In contrast, no significant association was found with stroke severity or etiology.

SD may not be the only type of sustained depolarization triggering migraine headache. In a recent prospective study on 200 consecutive adults with generalized epilepsy, 63% of subjects had a postictal headache following every seizure (Botha et al., 2010). According to the ICHD-II criteria, this headache was classified as a migraine headache in 47% and as probable migraine headache in 13% of subjects. Further subgroup analysis consistently revealed a highly significant relationship between postictal migraine headache and interictal migraine. Similarly to SD, IEEs may only trigger migraine headache if the patient carries a propensity to trigeminovascular pain.

However, propensities to trigeminovascular pain and to SD may not be entirely independent. Mice engineered to carry the CKId-T44A allele (cf. above) showed not only a reduced potassium threshold for SD but also a higher sensitivity to develop trigeminovascular pain in response to nitroglycerin, despite that nitroglycerin is not a trigger of SD (Brennan et al., 2013).

It might be added that whether or not SD will trigger migraine headache may also depend, for example, on cortical layers and regions been invaded (Karatas et al., 2013; Richter and Lehmenkühler, 1993) and on levels of SD-released noxious substances that discharge primary afferents.

Another question is whether SD without percept can trigger migraine headache in patients without aura. Electrophysiological proof of single SDs without percept in conscious and oriented stroke patients is very interesting in this respect (cf. above). However, the ^{133}Xenon SPECT studies in more than 30 carefully selected migraineurs without aura were not significant for spreading oligemia (Olesen and Friberg, 1991; Olesen and Meyer, 1991). Also, the firm association between ischemic stroke and migraine with, but not without aura (Kurth et al., 2012) rather supports the notion that migraine without aura is dissociated from SD.

Conclusions

The enormous bandwidth of clinical conditions involving SD makes it a phenomenon of major importance for brain pathology. The complex questions of when, whether and how SD should be treated, must be regarded in the context of the specific trigger driving it in a particular situation. Yet, the broad view of a stroke-migraine continuum provides a useful framework that can lead to new insights into relevant disease states. We therefore suggest that SDs are used as a common, clinically measurable denominator to define the class of neurological disorders in which SDs occur, in analogy to IEEs, which are already in clinical use since decades.

On this basis, non-invasive technologies to measure rCBF and its surrogates and cEEG should be further advanced to broaden the availability of information on SDs from non-surgical patient populations (Drenckhahn et al., 2012; Hartings et al., 2014). A caveat to consider though is that non-invasive technologies alone are not yet sufficient to reliably diagnose SDs. ECoG measurements with subdural strips currently remain the gold standard for monitoring SDs in patients, with the pros and cons of this approach as discussed in Box 3.

In close cooperation with basic and preclinical scientists, invasive neuromonitoring in neurointensive care units may be helpful in advancing the understanding of SD. This might improve disease characterization and stratification, which would

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Box 3.

Subdural strips are superior to depth electrodes for monitoring cortical activity in the context of SD because they are less invasive: depth electrodes cause cortical injury with upregulation of active inflammatory cell types and extravasation of plasma proteins into an area that is ~30 times the area of the physical insult (Liu et al., 2012). Moreover, subdural strips allow monitoring of a larger cortex region. Neither subdural strips nor depth electrodes require craniotomy but can be implanted through a burr hole, although it is recognized that the burr hole has to be somewhat more extended for the subdural strip (Dreier et al., 2009; Drenckhahn et al., 2012; Jeffcote et al., 2014). The basic recording quality seems similar but, in the cortical depth, electrodes are more likely exposed to large and complex changes in pH and tissue partial pressure of oxygen, which interfere with the potent catalyst platinum and should cause large disturbances of the DC signal.

allow more targeted treatments, following the concept of Precision ("individualized") Medicine, recently enunciated by the US National Academy of Science (National Research Council Committee on A Framework for Developing a New Taxonomy of Disease, 2011). It should be investigated for example whether a delayed, severe cluster of SDs in an individual necessitates the rigorous search for a typical etiology of secondary neurological deterioration such as (1) sepsis, (2) hypoglycemia due to an overdosing of insulin (Dreier et al., 2009), (3) systemic hypoperfusion (Hartings et al., 2009), or (4) delayed cerebral ischemia (Dreier et al., 2006). Identification of the underlying etiology would then be followed, if possible, by immediate treatment that specifically targets the identified etiology (e.g., with [1] antibiotics, [2] glucose or [3 and 4] catecholamine administration, respectively). Moreover, neuroprotective interventions targeting SDs such as hypothermia or pharmacological approaches could be selectively investigated in patients presenting delayed, severe clusters of SDs.

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