

1ST NENCKI SYMPOSIUM ON: JERZY KONORSKI CONTRIBUTION TO MODERN NEUROSCIENCE



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Symposium

JERZY KONORSKI CONTRIBUTION TO MODERN NEUROSCIENCE

**to commemorate this outstanding neuroscientist on the 40th anniversary of his death
and 95 anniversary of establishment of the Nencki Institute**

Bolek Srebro, University of Bergen, Bergen

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Emotional mechanics in limbic circuits

Ewelina Knapska, Nencki Institute of Experimental Biology, Warsaw

Social modulation of learning

Stephen Maren, Texas A&M University, Texas

Brain circuits for contextual control of fear

Organized by Andrzej Wróbel (chair), Ewelina Knapska, and Małgorzata Skup

Department of Neurophysiology, Nencki Institute of Experimental Biology

19 September, 2013 at the Nencki Institute of Experimental Biology

Reflections on Jerzy Konorski “Integrative Activity of the Brain” – nearly half a century after*

Bolek Srebro

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Konorski's monograph “Integrative Activity of the Brain” was published by The University of Chicago Press in 1967. Its Polish translation was published by PWN two years later. The book was a bold effort to summarize and conceptualize in neuroscientific terms then current state of knowledge on motivational and cognitive processes in the mammalian brain. It reviewed a large body of new experimental work on classical (Pavlovian) and instrumental (Konorski and Miller) conditioning, presented new results on transient (dynamic) memory and, finally, it proposed a grand model of integrative function of the brain. In my presentation I will review the background of the book and Konorski's motivation for writing it. After a short summary of the most important ideas presented in the book and I will try to relate and confront some of these ideas with the recent developments in brain sciences.

To some disappointment of the author, the book did not receive a worldwide attention as it probably deserved at the time of publication. One significant factor that might have contributed to this was Konorski's death a few years after publication of the book and hence his inability to provide an updating commentary. The other inevitable factor was an explosive development of brain sciences in the next decades which brought a wealth of new findings. Another possible factor is a general dislike of and empirical skepticism to any grand models. Looking back after almost half a century at the importance of Konorski's “Integrative Activity of the Brain” one can safely state that it was almost a “Summa Neurobiologica” of its time. Today this book belongs to a collection of documents on development of important concepts in modern neuroscience. Furthermore, some of the ideas presented in the book “seeped” into the subconsciousness of modern neuroscientists' and are still relevant today as this symposium will attempt to show.

*the full version of the review is available on pp 451–462 in this issue.

Gnostic cells in the 21st century**

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In this short review, I revise the notion of gnostic cells posited by Konorski, together with similar arguments by James, Lettvin and Barlow – namely, the idea of pontifical, grandmother and cardinal cells, respectively. I then discuss how the characteristics of the recently discovered concept cells, i.e. neurons in the human medial temporal lobe with a very high degree of specificity and invariance, fits the conjecture of gnostic or grandmother cells and then discuss the key role of concept cells in memory formation.

**the full version of the review is available on pp 463–471 in this issue.

Gradient-selective neurons: From single cells to human fMRI

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Gradient-selective neurons

Gradient-selective neurons were discovered in the nineties at the end of the Insight projects, supported by FET. Xiao and others (1997) showed that MT/V5 neurons were selective for linear speed gradients representing planes tilted in depth and relied upon their antagonistic surround for this selectivity, thus providing a mechanistic explanation. Subsequently, similar neurons were found in MSTd (Sugihara et al. 2002), and invariance for mean speed was demonstrated. The most complete description of speed-gradient selective neurons was provided by Mysore and colleagues (2010), who compared first and second-order speed-gradient selective neurons in MT/V5 and FST. Neurons were more selective and this selectivity was more invariant in FST compared to MT/V5, in agreement with the anatomical link between these two areas. Many of the second-order neurons in FST were selective for saddle-shaped surfaces, an intriguing finding. Given that many joints are in fact saddle-shaped, at least from certain view points, this suggests a manner in which shape signals can be injected into the motion stream to extract action-related signals, which combine motion and shape.

Similar gradient-selective neurons were also described for texture and disparity gradients. For texture only first order gradient selective neurons have been described in CIP (Taira et al. 2000) and TEs in infero-temporal cortex (Liu et al. 2004). First-and second-order disparity gradient-selective neurons have also been documented in the ventral (TEs, Janssen et al. 2000) and dorsal visual pathways (CIP, Taira et al. 2000; and AIP, Srivastava et al. 2009), and even in ventral premotor cortex (Theys et al. 2012). The ventral neurons play a role in discrimination (Verhoef et al. 2010), while those in the dorsal pathway likely analyze the 3D shape to control prehension (Sakata et al. 1995).

Using parallel functional imaging to extend knowledge to the human brain

In order to show that similar neurons exist in human cortical areas, we proceeded in two steps: demonstrating that in the model system, here the macaque, the presence of gradient-selective neurons can be captured by fMRI responses in a given paradigm, and then applying this paradigm in human subjects to identify the corresponding areas. As paradigm for investigating 3D structure from motion we introduced the comparison between viewing randomly-connected lines rotating in depth and those same lines translating in the fronto-parallel plane (Orban et al. 1999). It turns out that in the monkey this contrast activates only a few higher-order visual areas: notably MT/V5 and FST (Vanduffel et al. 2002). In fact, gradient-selective neurons in FST respond differentially to these two stimuli (Mysore et al. 2010) thus validating the paradigm. Recently, the human homologues of MT/V5 and some of its satellites have been mapped retinotopically (Kolster et al. 2010). Human MT/V5 and to some degree putative FST (pFST) are also activated by the comparison of rotating vs. translating random lines, suggesting that these areas house speed-gradient selective neurons, as do their monkey counterparts.

In the case of disparity, the fMRI data are even more impressive. Disparity gradient-selective neurons have been reported in TEs, AIP and ventral premotor cortex and all three areas show interactions in the fMRI (Joly et al. 2009) between the factors shape of the surface (flat vs. curved) and stereopsis (present /absent). The same interaction in humans (Georgieva et al. 2009) activates phAIP and DIPSA, which together represent the homologue of monkey AIP (its anterior motor and posterior visual side, respectively, Durand et al. 2009), as well as ventral premotor cortex. The absence of a temporal activation in that study is probably due to susceptibility artifacts that prevented recording fMRI responses in the anterior part of the temporal lobe. Thus there is reasonable evidence that disparity gradient-selective neurons occur in phAIP and ventral premotor cortex of humans.

Significance

Gradient selective neurons are a family of neurons which represent 3D surfaces as populations (for review see Orban 2011). They fall short of being gnostic units as Konorski (1967) defined them. However they go a long way in showing that the visual system of primates provides more powerful and complex analyses of the retinal image than generally assumed (for another example see Sary et al. 1993). Even if several of these neurons need to act together for uniquely representing a 3D surface, they indicate that visual neuronal populations can encode complex visual features and not just low-level features such as orientation, as is often assumed. It may well be that this is the rule in non-human primates, while the increase in size of the brain in humans may have allowed the development of grandmother neurons or gnostic units, at least for some very familiar visual objects. In this respect it is possible that the human hippocampus and medial temporal lobe (MTL) is very different from that of animals and certainly of rodents (Orban, in press). The expansion of the volume of this region as well as the change in the nature of afferent signals, may explain why the first recordings of single neurons in human MTL (Quiroga et al. 2005) were met by most neuroscientists with skepticism, because they only were familiar with animal results.

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Konorski's heritage: How Reactivity and Plasticity permit memory to anticipate the future

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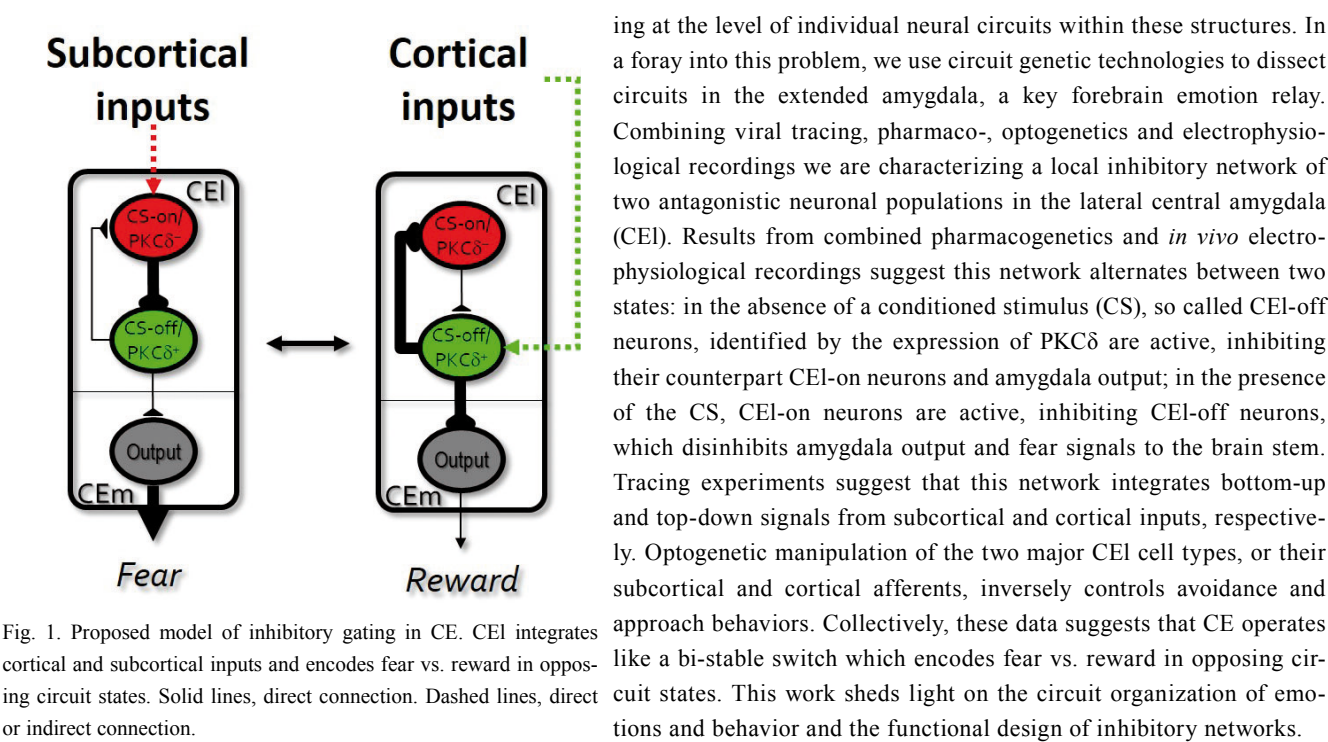
Powerful ideas often metamorphose and acquire new meaning as science advances. Jerzy Konorski (1948) recognized two metaprinciples that underlie the operation of the nervous system: Excitability (later renamed Reactivity, 1967), which is the capacity to be activated by stimulation of receptive organs, and Plasticity, which is the capacity to change reactive properties as a result of successive activations. Over half a century later, we can now attempt to evaluate, extend and translate these metaprinciples into distinct molecular, cellular and systems processes and mechanisms. Furthermore, new findings provide an opportunity to integrate these metaprinciples to propose how the brain, while reacting to the world, also anticipates it to render plasticity more parsimonious and reaction more efficient. This emerging dynamic and multilevel model of the brain impacts our understanding of the stability of memory, its veracity, and, furthermore, the biological bases and phylogenetic advantage of mental time travel to the future, i.e. imagination.

Emotional mechanics in limbic circuits

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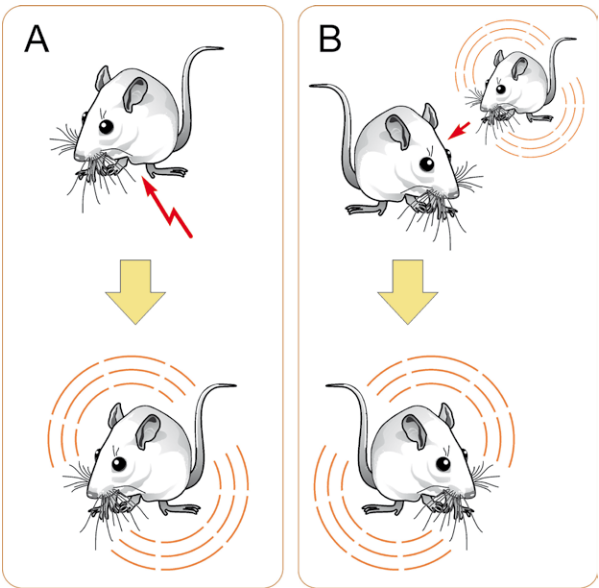
Emotions motivate behaviors necessary for survival, are central to our mental self and linked to a variety of psychiatric conditions. Not surprisingly, there has been a longstanding interest in deconstructing how emotions are wired in the brain. However, due to the brain's internal complexity, this turned out to be a formidable challenge: while the limbic system components have been known as major emotion centers for quite some time, it proved much more difficult to resolve the mechanics of information process-



Social modulation of learning

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ing at the level of individual neural circuits within these structures. In a foray into this problem, we use circuit genetic technologies to dissect circuits in the extended amygdala, a key forebrain emotion relay. Combining viral tracing, pharmaco-, optogenetics and electrophysiological recordings we are characterizing a local inhibitory network of two antagonistic neuronal populations in the lateral central amygdala (CEI). Results from combined pharmacogenetics and *in vivo* electrophysiological recordings suggest this network alternates between two states: in the absence of a conditioned stimulus (CS), so called CEI-off neurons, identified by the expression of PKC δ are active, inhibiting their counterpart CEI-on neurons and amygdala output; in the presence of the CS, CEI-on neurons are active, inhibiting CEI-off neurons, which disinhibits amygdala output and fear signals to the brain stem. Tracing experiments suggest that this network integrates bottom-up and top-down signals from subcortical and cortical inputs, respectively. Optogenetic manipulation of the two major CEI cell types, or their subcortical and cortical afferents, inversely controls avoidance and approach behaviors. Collectively, these data suggests that CE operates like a bi-stable switch which encodes fear vs. reward in opposing circuit states. This work sheds light on the circuit organization of emotions and behavior and the functional design of inhibitory networks.

Neuronal plasticity, a notion put forward by Jerzy Konorski, is very important for understanding changes in animal behavior, from the simplest responses to complicated interactions in social groups. It is well known that social behaviors are regulated, among other factors, by emotions and that the emotion displayed by a conspecific influences the behavior of other animals. However, the mechanisms by which the animals that are not directly endangered share emotions remain largely unknown. We developed a model of between-subject transfer of fear (Fig. 1), in which a naive rat interacts with its cage-mate, which was subjected to fear conditioning. In this models, the rats were kept in pairs and one animal (“demonstrator”) was treated to specific behavioral training of either foot-shock-reinforced context conditioning or just exposure to a novel context. The influence of the demonstrators on the brain activation and learning of their cagemates (called “observers”) were examined. Within this model of socially transferred fear, it was shown that several brain structures of the observers mirror the activity of the demonstrators’ brains (as revealed by c-Fos mapping), and that the observers have most of their amygdala and prefrontal cortex activated to the same level as the demonstrators and, in the case of the central amygdala, to an even higher level. In further development of the model, it was also demonstrated that a brief social interaction with a cage mate that has under-

gone an aversive learning experience promotes aversive learning in an otherwise naive animal. The reasoning that led to this conclusion is based on the following observations. First, during social interaction with a recently fear-conditioned partner, observers and demonstrators exhibit social exploratory behaviors rather than aggressive behaviors. Second, learning and memory in a shock-motivated shuttle avoidance task are facilitated in rats that underwent a social interaction with a partner that had been fear conditioned. Finally, a brief social interaction with a recently fear-conditioned partner immediately before fear conditioning increases conditioned freezing measured on the next day. In subsequent set of experiments, differences in both activation patterns within the limbic system and modulation of learning depending on the sex and estrus cycle phase were observed. In yet another paradigm, the IntelliCage automatic behavioral assessment system was used to study social interactions in more natural settings. The IntelliCage allows studying behavior of mice living in social groups over long periods of time, thus reducing social isolation and experimenter's exposure stress. In two different experimental settings we showed that the mice are capable of emotional information transfer. It was shown that the presence of a fearful cage mate results in a robust renewal of avoidance responses that were previously successfully extinguished. Moreover, it was observed that mice with spatial memory deficit were capable to learn normally when co-housed with the well-performing littermates, the result suggesting socially transferred information. The reported results are deeply rooted in the scientific heritage of Jerzy Konorski. His views about neuronal plasticity and instrumental reflexes still provide a useful guidance in planning, executing and interpreting the experiments. Of course, as knowledge is accumulated, the detailed research problems change. The reported results constitute an example how classic scientific concepts (Konorski's neuronal plasticity) conquer new research territories (social interactions) offering a logical framework for the incoming data (social modulation of neuronal plasticity).

Brain circuits for contextual control of fear

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While it is generally adaptive to rapidly learn about threats in the environment, this form of learning can lead to psychopathology including post-traumatic stress disorder (PTSD). In the clinic, exposure therapy is an effective method for suppressing pathological fear, but relief can be transient and prone to relapse. Recent work from my laboratory has explored the neural mechanisms underlying fear relapse after extinction, a form of learning that models exposure therapy in humans. Interestingly, extinction memories are labile and fear relapses upon the passage of time and changes in context. The return of fear after extinction is consistent with Konorski's proposal that extinction results in a new inhibitory memory that is formed alongside the excitatory fear memory. We have now identified a network of brain structures in the rat including the amygdala, hippocampus, and prefrontal cortex that contribute to regulation of fear responses after extinction. In particular, we show using electrophysiological and cellular imaging approaches that reciprocal hippocampal-prefrontal circuits control fear output by regulating amygdala neurons involved in fear expression.

Chosen abstracts from poster session accompanying the Symposium

TIMP-1 loaded nanoparticles: A therapeutic strategy for neuroprotection

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There is a marked deleterious increase in expression of Matrix Metalloproteinase-9 (MMP-9) during numerous pathologic conditions such as ischemic stroke, epilepsy and excitotoxic/neuroinflammatory processes. Therefore, inhibition of MMP-9 is considered as a potential therapeutic target for neuroprotection. Currently, available chemical inhibitors of MMP-9 are poorly specific and have wide range of off-targets leading to unanticipated side effects. As development of specific inhibitors is always a challenging task, therefore we planned to evaluate neuroprotective effects of an endogenous inhibitor of MMP-9, Tissue Inhibitor of Matrix Metalloproteinase-1 (TIMP-1), which is a 28 KDa protein. However, the major obstacles of using TIMP-1 as a neuroprotective agent are its short half-life *in vivo* and low brain permeability. Hence, we planned to explore a nanotechnological approach for delivery of TIMP-1, by using PLGA based Nanoparticles (NPs), so in the future it can be developed as a carrier of a neuroprotective agent.

Here, we have developed TIMP-1 loaded poly lactic-co-glycolic acid (PLGA) nanoparticles (NPs) which can deliver TIMP-1 in a sustained release manner and can cross the blood brain barrier (BBB). These NPs were coated with Tween 80 to improve their BBB penetration. We evaluated these NPs for their *in vitro* and *in vivo* BBB penetration by using primary rat brain endothelial cell model and by tail vein injection in mice respectively. The *in vitro* and *in vivo* results have shown that NPs are non-toxic to endothelial cells and that they penetrate BBB. Finally, we evaluated their neuroprotective effects on organotypic hippocampal slice culture using propidium iodide staining and LDH assay which have shown that TIMP-1 and TIMP-1 loaded have neuroprotective effects against Kainic Acid (KA) induced excitotoxicity. Moreover, we have shown through gelatinase assay that these effects are mediated through MMP-9 inhibition. In future, we would like to do further *in vivo* studies to evaluate pharmacological effects of TIMP-1 NPs.

Lack of strong cortical impact on the somatosensory evoked potentials recorded in the rat thalamus

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Local field potentials recording enables us to chronically monitor brain activity. However, electric field spreads widely through a brain tissue and due to this, signal recorded in one place may reflect synaptic currents from distant neuronal populations. In the rat vibrissae-barrel system the cortical representation of mystacial vibrissae is located closely above the region of somatosensory thalamic nuclei. Moreover, when activated by the sensory input, populations of cortical pyramidal cells generate evoked potentials (EPs) order of magnitude larger than can be observed in the thalamus. Since the dynamics of particular waves recorded in the thalamus resembles those of cortical ones, it is crucial to determine the impact of distant and local sources on the recorded signal. Using two linear multielectrodes (100 μ m inter-electrode distances) we recorded a series of potentials evoked by deflections of a group of large mystacial vibrissae, thus obtaining EP profile spanning the tissue from the cortical surface to the level below somatosensory thalamic nuclei. In order to find the activity sources specific for studied structures we analyzed the data using Kernel Current-Source Density method and Independent Component Analysis. We found, that EPs recorded within the thalamus were composed mainly of components characteristic to the local, thalamic sources. Distant cortical sources affected amplitude of the thalamic waves, but their impact on the shape of these waves was small. Maximum value of the amplitude of cortical potential sources at the level of the thalamus was estimated to be about 2.4% of maximum value of thalamic potential amplitude.

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Different neuronal circuits underlie recent and remote memory of fear extinction

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Hippocampal-prefrontal cortex-amygdala circuit is involved in formation of conditioned fear memory as well as fear extinction memory. Extinction of fear creates a new memory trace which can be modified by presentation of conditioned stimuli outside the extinction context (promoting fear renewal) or by the passage of time (spontaneous recovery phenomenon). In this study we were investigating involvement of each aforementioned brain structures in the retrieval of extinction memory in a changed context and after passage of time. We tested the conditioned fear response (freezing) 24 hours or 28 days after extinction session in the same or different context. Then, we mapped c-Fos expression in the prefrontal cortex (prelimbic and infralimbic parts), hippocampus and amygdala. We found that low level of freezing observed 24 hours after the extinction session (successful extinction) was associated with activation of the infralimbic cortex and ventral hippocampus. On the other hand, fear renewal (high freezing response) observed during testing in the changed context 24 hours and 28 days after the extinction session was associated with high level of the prelimbic cortex activation. Moreover, after 28 days additional activation of the infralimbic part of the prefrontal cortex appeared. Spontaneous recovery of fear (high freezing response) observed 28 days after the extinction session resulted in activation of neither the infralimbic nor prelimbic cortices. In all experimental groups we observed high activation of the basal nucleus. The presented data show that the neuronal circuits involved in fear renewal and spontaneous recovery are different, as well as that the fear extinction memory trace changes over time.

A computational model of learning, decision making and basic interactions of mice in IntelliCage

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It was shown that APPV717I transgenic mice (a model of Alzheimer's disease) have decreased ability to find the location of a reward (sweetened water provided in one of the cage's corners while pure water is provided in the others) as compared to wild type mice. However, if both strains are co-housed, transgenic mice perform as well as wild type mice. The performance of both strains also expresses circadian oscillations (Kiryk et al. 2011).

We employed a number of computational models of behavior (Daw 2011) to identify a specific mechanism responsible for observed behavior. The simplest model investigated was a Q-learning model using the Rescorla-Wagner rule for learning of expected outcomes of actions (visits in particular corners). Decisions depend only on the learned values (the probability of visiting a particular corner is given by the softmax distribution).

The model captures the trend of the learning curve well, but does not explain its oscillations. However the same model modified to take into account blocking of a corner by an animal already occupying it exhibits the oscillations.

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