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Short communication

Poised for survival: Criticality, natural selection, and excitation-transcription coupling

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ABSTRACT

Neurologically-complex species utilize two intricately coupled information-processing systems to adapt to their social and natural environments. Action potentials (APs) facilitate rapid responses to the nearly continuous fluctuations in the animal's surroundings. By contrast, genetic encodings comprise a molecular memory of ancient adaptive responses expressed as cognitive, emotional, or behavioral phenotypes. The linking of the two systems via intracellular Ca^{2+} networks which address transcription factors – e.g., cAMP response element-binding protein (CREB) – is an appropriate focus for the biology of human behavior. Computational modeling utilizing Boolean networks (BNs) is a suitable qualitative method, requiring no kinetic information, for eliciting the systems' architectural properties. In particular, BNs can reveal critical intracellular regimes of possible evolutionary significance. As a platform for future research, we propose that those networks sufficiently robust to attenuate damaging intracellular noise and deleterious mutations, yet sufficiently close to chaos to permit or amplify adaptive noise and favorable mutations, would be favored by natural selection. Critical regimes of this type would be, literally, "poised for survival", and would stabilize and promote the survival of their correlated cultural phenotypes.

1. Introduction

The neuron is rich with codes. In all behaviorally complex species, action potentials (APs) encode sensory input, correlate it with relevant cognitive, autonomic, and emotional data, and convert the computations into behavioral output. This swift response is adaptively useful given rapid fluctuations in an animal's surroundings. By contrast, neural DNA encodes cognitive and behavioral phenotypes which facilitated survival during the animal's evolutionary history. The two systems are not discrete: Activity-dependent, Ca^{2+}-mediated intracellular signals phosphorylate transcription factors (e.g., cAMP response element-binding protein (CREB) which activate targeted genes, initiating transcription, and ultimately modifying synaptic morphology. Synaptic modifications in turn dampen or amplify correlated cognitive and behavioral processes. The current behavioral signatures of all living complex animals – including, importantly, humans – and their evolutionary histories are thus intricately mixed.

In this article, neuron–gene reciprocal signalling – more generally known as excitation-transcription (E-T) coupling – is designated as a critical component of the evolutionary biology of human cognition and behavior. Traditional approaches to this topic, e.g., behavior genetics and evolutionary psychology, have frequently been inferential, relying on indirect evidence. In behavior genetics, for example, claims of genetic influence are based on comparisons of monozygotic twins, dizygotic twins, and unrelated people; these are currently the subject of an intense debate regarding heritability measures and underlying molecular mechanisms (Hamer, 2002; McGue, 2008). Addressing these issues, Kremen and Jacobson (2010) call for cross-disciplinary research linking genetics, neuroscience, psychology, and psychiatry "in order to be able to trace the pathways between genes, brain, and behaviour". Similarly, in evolutionary psychology (Tooby and Cosmides, 1992), claims of evolutionarily specialized brain information-processing systems ("modules") only rarely link the putative modules to underlying neural and genetic substrates (Bolhuis et al., 2011). Accordingly, Panksepp et al. (2002) observe that "modern neuroscience has provided a suitable foundation to begin thinking more clearly about the underlying organic basis of mental processes. Molecular biology is now providing equally fruitful approaches for uncovering the functional characteristics of biological systems that are inherited via genetic transmission. The social sciences must deal with such underlying levels of organization and some have started to do so, albeit at a markedly slow pace." The present article concurs with these criticisms, and suggests that future models in behavior

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genetics and evolutionary psychology should be informed by investigations of the "dialog between genes and synapses" (Kandel, 2001). Analyses of E-T coupling via human neuronal cell cultures (Hynd et al., 2003; Dedova et al., 2009) together with molecular imaging studies (Collins et al., 2012; Hong et al., 2013), and the rapidly expanding investigations in evolutionary neurobiology (Barger et al., 2007, 2012), can empirically strengthen behavior genetics and evolutionary psychology, and thereby generate an enhanced understanding of the roots of human behavior.

Below we will briefly examine a relatively well-documented example of Ca^{2+}-mediated E-T coupling in a system for which there exist convergent molecular, clinical, and evolutionary data sets: CREB signaling in amygdala neurons (Lonze and Ginty, 2002; Josselyn, 2010). We will acknowledge the intricacy of Ca^{2+} networks, and note two major computational approaches to accommodate the complexity: continuous-modeling methods utilizing ordinary differential equations (ODEs), and discrete modeling utilizing Boolean networks (BNs) (Moraru and Loew, 2005; Bornholdt, 2008). Although each method has its advantages, we will emphasize BNs as a powerful qualitative strategy which requires no kinetic parameters, but nonetheless can provide testable models of molecular systems comprised of hundreds of components (Wang et al., 2012; Davidich and Bornholdt, 2008). In addition, because BNs may be used to study the "interplay between the structure and dynamics of complex multi-level systems" (Cozzo et al., 2012), we suggest that they are well-suited to examine human behavior from the molecular to the cultural level. We propose that the use of BNs together with studies of actual neurons (Adolphs, 2010; Freeman et al., 2010), and archeological data sets (Barger et al., 2007, 2012; Foley and Gamble, 2009) may yield valuable insights into the evolutionary neurobiology of human cognition and behavior. As a programmatic example, we present the following hypothesis: Neuron molecular networks sufficiently robust to reduce deleterious mutations and damaging intracellular noise, yet sufficiently close to chaos to permit favorable mutations and beneficial molecular noise, would be preserved by natural selection. These poised intracellular molecular networks – ordered, but on the edge of chaos, i.e., at criticality – would in turn promote the survival of their correlated behavioral, emotional, and cognitive phenotypes.

2. Excitation-transcription coupling in the amygdala

Describing E-T coupling presents a methodological challenge (Wheeler et al., 2008). Unlike other biological responses induced by excitability (e.g., excitation-contraction (E-C), and excitation-secretion (E-S) coupling), input in E-T coupling (Ca^{2+} channel gating) is widely separated, spatially and temporally, from output (gene expression). The distance from synapse to nucleus may be tens of micrometers, while gene expression may occur minutes or even hours following Ca^{2+} influx. Moreover, methodologies used to study electrophysiological processes such as channel gating differ markedly from approaches used to study biochemical systems such as transcription-factor phosphorylation. Consequently, there is only one well-studied example of E-T coupling in neurons: Ca^{2+} signaling to the CREB transcription factor (Fig. 1). Fortunately this system has also been studied in the amygdala (Josselyn, 2010), for which convergent human evolutionary (Barger et al., 2007, 2012) and clinical data (Adolphs, 2010) are also available.

CREB activation is initiated at the neural membrane (Lonze and Ginty, 2002; Carlezon et al., 2005; Cohen and Greenberg, 2008). Ca^{2+} enters the cytosol through two major input systems: the ligand-gated *N*-methyl-D-aspartate receptor (NMDAR) channel, and the L-type voltage-gated calcium channel (LVCC). (A putative third Ca^{2+} input, the endoplasmic reticulum, may be more closely related to mitochondrial Ca^{2+} uptake and ATP production than CREB targeting and gene expression (Lam and Galione, 2013). Following channel gating, Ca^{2+} binds with a wide range of intracellular molecules, involving extensive cross-talk, of which calmodulin (CaM) is the best characterized. A molecular hub for Ca^{2+} signaling, CaM activates the Ca^{2+}/calmodulin-dependent protein kinases CaMKI, CaMKII, and CaMKIV, each of which has the capacity to phosphorylate CREB at Serine (Ser) 133. CREB phosphorylation activates binding of the CREB kinase-inducible domain (KID) – of which Ser 133 is a component – with the kinase-inducible domain interacting (KIX) domain of CREB-binding protein (CBP), initiating gene expression. CBP, a histone acetyltransferase (HAT), together with the HAT coactivator p300, transfers acetyl groups to histones, causing chromatin to adopt a more relaxed conformation in which stretches of DNA are made accessible to transcription. Identification of amygdala genes targeted via CREB is in its early stages, based largely on a pioneering microarray study utilizing a rat model (Ploski et al., 2010). The study examined CREB activation via the evolutionarily highly conserved synaptic- and Trk-activated extracellular receptor kinase (ERK)/mitogen-activated kinase (MAPK) pathway. Seven plasticity-associated genes (Fos, Atf3, Egr2, Arc/Arg3.1, Gadd45g, Nr4a2, and JunB) were significantly expressed following Pavlovian fear conditioning (but see functional discussion below).

Post-translational events in which plasticity-related proteins (PRPs) modify synapses, thereby completing the E-T circuit, are currently the focus of intensive research. One model suggests that molecular "tags" – possibly tyrosine kinase B (TrkB) – localized at presynaptic terminals – recruit PRPs during memory stabilization (Frey and Morris, 1997; Lisman and Raghavachari, 2006; Lu et al., 2011). Simultaneously, upregulated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptors (AMPARs) are anchored to the postsynaptic density (PSD) via a pool of PRPs. Importantly, if memory stabilization via long-term-potentiation (LTP) is insufficient; AMPARs are exocytosed, returning the PSD to baseline levels. Viewed as an adaptive information-processing system, AMPAR exocytosis is one of several negative-feedback loops in CREB-based E-T signaling that modulate synaptic strength, thereby facilitating network updates. Other loops would include HDAC1 (histone deacetylase 1)- and HDAC8-associated protein phosphatase 1 (PP1) which de-phosphorylates CREB at Ser-133 (Lee and Silva, 2009), endogenous inducible cAMP early repressor (ICER) which competes with CREB for CRE binding sites (Mioduszewska et al., 2003), and CREB phosphorylation at Ser-142 via CaMKII which blocks CREB-mediated transcription (Wu and McMurray, 2001).

New studies of phenotypic correlates of CREB signaling in the amygdala reflect a revised functional interpretation which in turn appears consistent with brain evolutionary studies. Increasingly problematic is the exclusive identification of the amygdala with negative emotions, e.g., a "fear module" (Ohman and Mineka, 2001). The viewpoint cannot easily accommodate the increasing anatomical evidence for a wide range of cortical and subcortical inputs conveying sensory, nociceptive, and affective information – assuredly including fear – but also including positive emotions (Murray, 2007; Pessoa and Adolphs, 2010). More consistent with the anatomy is the "emotional salience" model in which the amygdala is proposed to process biologically-relevant features of environmental stimuli including, importantly, conspecifics (Adolphs, 2010; Pessoa and Adolphs, 2010; Pessoa, 2010; Gonzales Andino and Grave de Peralta Menendez, 2012). Notably, although ~70% of amygdala neurons receive sensory input in auditory conditioning in an animal model, only ~25% display auditory-induced plasticity (Zhou et al., 2009). Is CREB involved in this selective process? Imaging CREB-injected mouse amygdala neurons via activity-regulated cytoskeleton (Arc) protein mRNA indicated ~10 times greater probability to be activated in a learning paradigm