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## Altered States of the Human Mind: Implications for Anthropogeny

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**Jean-Pierre Changeux**, Collège de France & Institut Pasteur

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### ABSTRACTS

#### ***Psychedelics***

**Frederick Barrett**, Johns Hopkins School of Medicine

Psychedelic drugs such as psilocybin and LSD have re-captured the imagination of both popular society and modern science. We will briefly review the history of psychedelic research and sample current empirical knowledge regarding the acute effects of classic psychedelic drugs on perception, cognition, emotion, and brain function. We will then briefly review the potential therapeutic efficacy of psychedelic drugs. We will end with a discussion of potential mechanisms underlying acute and enduring effects of psychedelic drugs, and a reflection on what psychedelic drugs might be able to teach us about consciousness.

#### ***Cognitive Enhancement (Nicotine, Caffeine, Cocaine, Amphetamine) and General Anesthesia*** **Jean-Pierre Changeux**, Collège de France & Institut Pasteur

Cognitive enhancers or psychostimulants are pleasurable and invigorating molecules claimed to alter the state of the human mind by stimulating cognitive functions, memory, creativity or motivation, without causing major hallucinations. They include nicotine, caffeine, cocaine, amphetamines... In contrast, general anesthetics (GAs) cause a decreased awareness to painful stimuli and a loss of consciousness. They include propofol, etomidate, isoflurane, benzodiazepines, and barbiturates.

Nicotine is used by Aboriginal groups to excite their courage, particularly in warfare. Andean workers use cocaine to reduce fatigue, improve mood, and even enhance sexual vigor. Most cognitive enhancers are structural homologs of brain neurotransmitters and target the chemical synapse. Nicotine and caffeine bind to the active site of neurotransmitter receptors: the nicotinic acetylcholine receptor for nicotine and the adenosine receptor for caffeine. On the other hand, cocaine and amphetamines block presynaptic transport and cause accumulation of excitatory neurotransmitters like dopamine at the synapse. In contrast, GAs act as allosteric modulators mainly of inhibitory GABA<sub>A</sub> receptors and enhance cortical inhibition.

The connectomic architectures engaged in cognitive enhancement and anesthesia are accounted for the Global Neuronal Workspace (GNW) theory of conscious access. These architectures are grounded on a reciprocal network of pyramidal neurons with long range axons which globally and reciprocally broadcast signals to (and from) multiple brain areas. Enhancers would cause a global activation of the GNW and GAs its down regulation. A causal link would then be established between the molecular targets of the drugs and the altered states of the human mind.

## ***Imagination and Embodiment in Practices of Sacred Sonorous Being***

**Thomas Csordas, University of California, San Diego**

Imagination is a fundamental human process. Can we then say that imagining is an altered state of consciousness, or is it the default state of consciousness that is the norm and defines us as human? In this presentation we recognize imagination as deeply embodied, and that as bodily beings we both hear and produce sound. In particular, I offer a reflection on the religious implications of our “sonorous being,” a phrase from the philosopher Maurice Merleau-Ponty. The sonorous being of our embodied, fleshly existence can give us insight into the imaginative generation of sacred power if we take it up in the context of concrete examples. Accordingly, I introduce two ethnographic phenomena that extend the existential meaning of our sonorous being to the dimension of the sacred. These are the religious practices of Pentecostal-Charismatic singing in tongues and Native American Church peyote songs. These ritual practices share the characteristic of singing without any semantic or lexical component, allowing us to reimagine vocalization, speech, and song as bodily secretions, or material emanations of sonorous being. The religious setting consecrates the natural act of vocalization as an imaginative act. I conclude by suggesting that these sacred songs create a particular relationship between immanence and transcendence. Engendering this relationship in concrete experience is the significance of peyote songs and singing in tongues, and what they have most in common in addressing the imaginative force of sonorous being in defining our humanity.

## ***Alcohol Metabolism and Alcoholism***

**Kenneth Kidd, Yale School of Medicine**

The first gene strongly associated with alcoholism was *DRD2*. It was a false association because the alcoholics were mostly Mexican Americans and the controls mostly European Americans. Our studies showed that the variant that “caused” alcoholism has its highest global frequency in Native Americans and a relatively low frequency in Europeans. That work started a quest to study more broadly the population genetics of susceptibility to alcoholism. Some of the strongest associations are with genetic variants that alter ethanol metabolism with the primary effect of providing resistance to alcoholism. The frequencies of the variants have different global patterns. Several of the individual genes in the alcohol dehydrogenase family of genes are involved, and the most studied variant is widespread with higher frequencies in East Asia and Southwest Asia. The aldehyde dehydrogenase 2 locus has a particularly sharply defined variant pattern with high frequency in Southern coastal China, lower frequency most everywhere else in East Asia, and absent elsewhere. Genomic analyses argue that positive selection is responsible for the high frequencies of these variants but fail to illuminate the selective force. Details of the population studies of these and other genes will be presented.

## ***Addiction and Loss of Control: Hyperkatifeia, Negative Reinforcement and the Dark Side of Addiction***

**George Koob, National Institute on Alcohol Abuse and Alcoholism; National Institute on Drug Abuse**

Drug addiction is a chronically relapsing disorder characterized by loss of control and compulsive drug seeking within a heuristic framework comprised of a three stage addiction cycle. Such loss of control is hypothesized to derive from multiple sources of motivational dysregulation that occur in three functional domains that reflect the three stages of the addiction cycle: incentive salience/pathological habits in the binge/intoxication stage, negative emotional states in the withdrawal/negative affect stage, and executive function deficits in the preoccupation/anticipation stage. These three domains and stages are hypothesized to be mediated by three major neurocircuitry elements: basal ganglia, extended amygdala, and prefrontal cortex, respectively. A largely neglected source of loss of control in addiction is the via the construct of negative reinforcement driven by the emotional pain of drug withdrawal and protracted abstinence. The construct of negative reinforcement, defined as drug taking that alleviates a negative emotional state or hyperkatifeia (pain, hypohedonia, dysphoria, anxiety, hyperalgesia, irritability, and sleep disturbances) associated with drug abstinence following excessive drug taking. Such hyperkatifeia that drives negative reinforcement is hypothesized to derive from loss of function of key neurochemical

circuits within the brain reward system in the basal ganglia and gain of function within the brain stress systems (corticotropin-releasing factor, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids and neuroimmune factors) in the extended amygdala. Compelling evidence exists to argue that hyperkatifeia triggered by acute excessive drug intake, is sensitized during the development of compulsive alcohol taking with repeated withdrawal, persists into protracted abstinence, and contributes to the development and persistence of compulsive, loss of control drug seeking. Significant overlap in the engagement in addiction of circuits mediating brain emotional pain and brain physical pain may help explain the prominent role of drugs in “deaths of despair” and the effects of social isolation on drug seeking in the covid-19 pandemic.

***The Neural Underpinnings of Mindfulness***  
**Read Montague, Virginia Tech**

Mindfulness meditation has recently seen an explosion in the number and variety of its practitioners and its application domains. It has been deployed in settings ranging from stress reduction therapies to concentration-and-focus in athletic endeavors. Mindfulness meditation has even shown strong promise in the area of neuromotor disease where motor symptoms and the stress they induce can be reduced significantly. Our group has focused on the neural underpinnings that support some of the behavioral features of mindfulness training including a capacity to disconnect brain regions that link valuation and responses to negative social outcomes. I will highlight how these experiments are being carried out using functional imaging and point the way toward future work using more fine-grained neural probes to understand mindfulness in terms of cognitive control.

***Peripartum Depression***  
**Barbara Parry, University of California, San Diego**

Major depression (MD) occurring during pregnancy, or postpartum, can be a devastating illness that impairs the ability of the mother to care for her infant, disrupts the family, and adversely affects the healthy physical, behavioral, psychosocial and neurocognitive development of the child. Maternal depression increases the child’s risks for mental and medical disorders later in life, contributes to cognitive and socio-emotional impairments at 5 years, and after 13 years, to higher rates of mood and anxiety disorders in adolescence. After 20 years, the risks for anxiety disorders, major depression, substance dependence, social impairment, medical problems and mortality are higher in the offspring of depressed parents compared with the offspring of non-depressed parents. Remission of maternal depression after three months of medication treatment, however, is associated with a decrease in children’s symptoms and diagnoses.

These findings emphasize the critical importance of treating peripartum depression. Safe and efficacious pharmacological treatments, however, are limited by potential adverse effects on the fetus or breast-feeding infant and psychotherapeutic interventions by time, expense and clinician availability. Light treatment improves mood, although significant antidepressant effects may not occur until after five weeks of intervention in this non-seasonal depression. In our previous work in pregnancy and postpartum depression, we observed improvements in mood with critically timed wake therapy and light treatment administered independently. Although wake therapy exerts its antidepressant effects in 1-2 days, patients may relapse after a night of recovery sleep. As reported in other mood disorder patients, the advantage of combining wake and light treatment is that one night of wake therapy can improve depressive symptoms in one day, and hasten and potentiate the antidepressant effects of light treatment to within one week. In turn, light treatment can prevent the relapse from wake therapy that often occurs after subsequent sleep. We have applied these combined chronotherapeutics to pregnancy and postpartum depression to achieve efficacious, rapid-acting, affordable home interventions with minimal side effects, and now aim to integrate these treatments into community practice for peripartum women with mood and sleep disturbances.

Based on our previous work, we hypothesize that chronobiological mechanisms underlie these treatment effects: In pregnancy MD, we observed phase-advanced (shifted earlier) melatonin circadian rhythms, and sleep and light interventions (SALI) that restricted and shifted sleep later (early-night wake therapy-EWT: sleep 3-7 am) plus evening (PM) bright white light (BWL), which phase-delayed (shifted-later) melatonin rhythms, improved mood and sleep. In contrast, in postpartum MD, we observed phase-delayed melatonin rhythms, and SALI that restricted and phase-advanced sleep (late-night wake therapy-LWT: sleep 9pm-1am) plus morning (AM) BWL, which phase-advanced melatonin rhythms, improved mood and sleep. We also found that when combined with wake therapy, 1-2 weeks of 30 min/day of light treatment was as efficacious as 6 weeks of 60 min/day.

The significance of this work is that it may provide novel, safe, efficacious, rapid-acting, affordable home treatments without significant side effects for women suffering from pregnancy or postpartum mood and sleep disturbances, prevent their adverse sequelae, and be acceptable and feasible to disseminate and implement in community vs. hospital or clinic settings.

### ***Altered States in Human Rituals***

**Ann Taves**, University of California, Santa Barbara

If we adopt fairly mainstream definitions of both ritual and altered states of consciousness (ASCs), it is clear that they intersect in some cases but not others. Rituals, whether religious or not, only induce noticeably altered states if the ritual includes “induction techniques,” which many rituals do not. When rituals do involve the induction of ASCs, it tends to stabilize them and reinforce their value

### ***Intersectional Neuroscience: Meditation and Diversity***

**Helen Weng**, University of California, San Francisco

Academic psychology and neuroscience have typically centered viewpoints of the dominant culture (WEIRD: Western, Educated, Industrialized, Rich, Democratic), which has influenced both the process and content of contemplative neuroscience. By incorporating more diverse perspectives through a lens of social justice, I present an Intersectional Neuroscience framework that center viewpoints of meditators who belong to minority groups, and use contemplative practices to heal identity-based suffering and build community. I highlight two main approaches to studying this deep contemplative work: 1) community engagement to incorporate diverse perspectives and participants, and 2) individualized multivariate neuroscientific methods to measure meditation skills, which rigorously measure diverse mental states within and between individuals. Community engagement with the East Bay Meditation Center was used to culturally-adapt research procedures for racial and ethnic minorities, LGBTQIA+ people, people with disabilities, the fat community, and people with less income. Importantly, community members were involved at each step, thereby empowering groups that have been historically oppressed in scientific research. To accommodate experiential and neural diversity, we designed the EMBODY Task which uses individualized machine learning applied to functional MRI data to measure diverse mental states during meditation. Machine learning classifiers were trained to learn and recognize brain patterns associated with internal attention states (breath attention, mind wandering, and self-referential processing), and then used to “read the mind” during meditation by estimating the internal focus of attention second-by-second. The EMBODY Task honors each individual’s unique brain structure and function, and provides novel metrics of attention during meditation (such as time attending to the breath) that can be analyzed at the group level. These methodological advances not only improve research in diverse populations but enhance the scientific rigor for the entire field. Throughout, I will highlight the importance of cultivating diverse scholars for enriching the field of contemplative research.