

Biology of Drug-Addiction

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Abstract: Drug addiction is a chronic, recurring and complex disorder in which use of substance is continued despite catastrophic negative consequences. It is a complex disease of the brain with anomalous behaviours linked to neurological alterations, and modulated by genetic, developmental and environmental factors. Amygdala, prefrontal cortex, Nucleus Acumbens, Hippocampus and Ventral Tegmental Area are implicated in addiction. This paper presents the recent understanding of neurological, neuro-circuitary, and neuropharmacological processes implicated in drug addiction.

Keywords: Reward circuit, Dopamine, Neuro-plasticity, Negative re-inforcement.

Drug addiction refers to continued use of substance despite catastrophic negative consequences¹. It is increasingly recognized as a neurobiological illness whereby repetitive drug use corrupts and reorganizes the normal circuitry of rewarding and adaptive behaviour². There is continued vulnerability to relapse even after an extended period of sobriety and a reduced drive to acquire biologically relevant natural rewards important for survival and optimal psychosocial functioning in the society³.

Addiction is marked by long-term remitting and relapsing course and caused by a complicated set of interactions such as genetic vulnerability, biochemical changes and high novelty-seeking, it is understood as chronic brain illness. In view of all these patho-physiological and clinical sign-posts, drug addiction can be defined as a chronic, often relapsing and complex disease process of the brain resulting from recurring drug-intoxication and modulated by genetic, developmental, experiential and environmental factors. It causes compulsive drug-seeking and using despite harmful consequences. It is a brain disease as the drug leads to changes in structure and function of the brain. Initial decision of drug-intake may be voluntary but repeated drug exposure affects person's self-control and ability to make sound decision⁴.

To understand the neurobiological basis, underlying neuro-circuitry and neuro-pharmacology involved in biological rewarding adaptive behaviour needs to be examined.

NEUROBIOLOGY OF REWARD

Organisms possess adaptive, evolutionarily determined systems that mediate acquisition of pleasurable rewarding behavior needed for survival i.e. sex, food and social affiliation and avoidance of aversive events. Three brain areas mediate such adaptive behaviour: the nucleus accumbens which mediates reward related activities (positive valence); the amygdala involved in fear motivated behaviour (negative valence) and the prefrontal cortex involved in decision making and prediction of rewarding behaviour by determining salience attribution of environmental stimuli and directing the intensity of the behavioural response⁵. A balanced functioning of motivational and affective states combined with external stimuli that predict reward, determine the overall output of a given behavioural response in acquiring natural reward^{6,7}.

WHAT HAPPENS TO THE BRAIN WHEN DRUG IS TAKEN?

Drugs tap into brain's communication system and disrupt the normal functioning of the brain cells – their sending, receiving and processing information. There are two ways a drug can disrupt normal cell functioning:

- 1.) By imitating the brain neurotransmitters
- 2.) By over-stimulating the "reward circuit" of the brain.

Some drugs such as marijuana and heroin have structural similarity to some neurotransmitters naturally produced by brain and fool the brain receptors and activate the nerve cells to send abnormal messages.

Some drugs such as cocaine and methamphetamines stimulate the nerve cells to release abnormally large amounts of natural neurotransmitters or prevent normal recycling of these brain chemicals. It produces greatly amplified messages and disrupts normal communication pattern.

Almost all addictive drugs target the brain's reward system by flooding the circuit with dopamine. These drugs activate the mesolimbic dopamine system which reinforces both pharmacological and natural rewards. The mesolimbic system consists of dopaminergic neurons in the ventral tegmental area (VTA) and their axonal projections to terminal fields in the nucleus accumbens (NA) and the prefrontal cortex (PFC). Addictive drugs act on this system to increase synaptic levels of dopamine (DA). These drugs have specific receptors in the brain and increase in dopamine levels in the mesolimbic system is the final effect produced by them.

DOPAMINERGIC PATHWAY

Reward: It is widely accepted that increased levels of dopamine in the nucleus accumbens mediate the reward effects or positive reinforcement of addictive drugs⁷. In experimental mice, who had been knocked out of D2 receptors, alcohol and morphine were found no longer rewarding. In humans, in a series of neuroimaging studies using cocaine or methylphenidate that increased dopamine levels in the brain were associated with euphoria and pleasure⁸. Low levels of dopamine D₂ receptors in drug-naïve individuals when administered methylphenidate, were found to be associated with pleasure, whereas high receptor levels in drug-naïve individuals were found with unpleasant feelings.

Anticipation: The role of dopamine in addiction is critical in anticipation and withdrawal as well. In primates trained to associate a cue with a pleasurable experience (food), increased dopaminergic activity was seen in response to the cue and not to the food⁹. If the food was not then presented, dopaminergic function dropped.

Reduced dopaminergic function is associated with negative affect (e.g. dysphoria). Thus, an individual with an addiction may see a 'cue' (e.g. a public house, mirror or needle) and if their drug of choice is not available may feel dysphoric, which is likely to increase the drive to obtain the drug.

Withdrawal: Reduced dopaminergic function has been seen in withdrawal and early abstinence from many addictive drugs.

Neuroimaging studies in cocaine, opiate and alcohol addictions have revealed reduced levels of dopamine D₂ receptors, which may recover to some extent during abstinence, but have been shown to persist for months⁷. Early stages of abstinence are associated with elevated levels of craving, drug-seeking and risk of relapse and it is likely that hypodopaminergic function plays a mediating role. Presumably the release of dopamine produced by the drug of choice provides relief from withdrawal, although this needs to be authenticated.

Because of the pre-eminence of the dopaminergic reward system in addiction, this has been a target for pharmacotherapy, but with mixed results¹⁰. In cocaine

addiction, the development of dopaminergic partial agonists at the D₃ receptor, such as BP-897, currently holds some promise. In rats, BP-897 inhibits cocaine-seeking behaviour in response to cues¹¹. As a partial agonist, this drug stimulates the D₃ receptor enough to keep withdrawal at bay, but not enough to cause a 'high' or to be rewarding. It is currently in phase 1 trials. One drug that affects the dopaminergic system and has proven efficacy in the treatment of nicotine addiction is bupropion¹². The exact mechanism underlying this effect still needs to be fully understood; however, it has been shown that bupropion increases dopamine and noradrenaline levels by acting as an uptake inhibitor¹³.

NEUROBIOLOGY OF INITIATION OF DRUG ADDICTION

All addictive drugs increase extra-cellular dopamine levels in nucleus accumbens either directly by enhancing dopaminergic transmission through reuptake inhibition or facilitating presynaptic dopamine release (ie cocaine, amphetamines) or by indirect mechanisms that affect dopamine cells firing (ie alcohol, opioids, nicotine cannabis)¹⁴.

Though dopamine is the primary mechanism of the initiation of drug reinforcement, other neurotransmitters have been implicated indirectly in acute reinforcing properties such as Gamma- Aminobutyric Acid (GABA), opioid peptides, acetyl choline, endocannabinoids and glutamate¹⁵. GABAergic interneurons provide afferent inhibitory modulation on the release of dopamine in the ventral tegmental area and nucleus accumbens and the drugs that enhance GABAergic functions are used in treatment of drug addiction^{16,17}.

Opioids modulate the activation of mu opioid receptors to increase dopamine transmission by inhibiting GABAergic interneurons¹⁸. The opioid system is also implicated in reinforcing properties of alcohol and cannabis and may play role in impulse control disorder¹⁹. It is believed that serotonin compounds possibly modulate the mesolimbic dopamine pathway²⁰.

Cholinergic neurons from the pedunclo-pontine or latero-dorsal tegmental nucleus provide excitatory input to the ventral tegmental area causing release of dopamine in the projection from the ventral tegmental area to the nucleus accumbens²¹. Nicotine cholinergic $\alpha 4$ - $\beta 2$ receptors have been strongly implicated in reinforcing properties of nicotine, whereas M5 muscarine receptors have been implicated in the rewarding effects of opioids and cocaine¹⁹.

Cannabinoid type I (CB1 receptor) mediates the reinforcing properties of cannabinoids that facilitate the release of dopamine in the nucleus accumbens²².

Excitatory glutamatergic input from various cortical structures (including prefrontal cortex) stimulates dopamine release in the ventral tegmental area and nucleus accumbens²³.

Dopamine, Nucleus accumbens and Neuroplasticity: addiction as a disease of pathological learning and memory

Neurobiological mechanism of learning and memory is corrupted by addictive drugs resulting in maladaptive learning associated with drug-related stimuli.^[15] Regarding natural rewards and adaptive behavioural responses, burst firing of dopamine neurons in nucleus accumbens begins a process of reward related neuroplasticity or learning that initially serves to alert that a novel salient stimulus has been encountered and start to encode this event.²⁴ As the motivational behaviour becomes learned and familiar, dopamine release is no longer induced by this fully predicted reward but instead occurs in response to the most distal conditioned stimuli that come to predict the rewarding event²⁵. Therefore, dopamine alerts the individual through associative learning that a natural reward is coming or that a adaptive behavioural response can be predicted, and dopamine release gets transferred from motivational to neutral stimuli. This is in contrast to addictive drugs that are able to increase nucleus accumbens dopamine levels far greater than that of biologically rewarding stimuli and continue to release elevated

dopamine levels up to each drug administration. This pharmacologically induced, enhanced, and sustained dopamine increase relative to biological stimuli causes more intense learned association with neutral environmental stimuli; and the brain gets the message that these events are "better than expected" and that drug related stimuli would theoretically be associated with a more intense stamping in environmental stimuli that come to predict reward over biologically relevant ones¹⁶. This "over-learning" of drug acquisition behaviour plays a significant role in initiation of addiction cycle. It explains enhanced vulnerability to craving and relapse by cue-induced environmental triggers²⁶.

Transition from reward to addiction: hypothalamicpituitary- adrenal axis and the stress-system: Withdrawal and negative reinforcement

Addictive drugs activate the brain stress-system and lead to elevated adrenocorticocortrophic hormone, corticosterone and corticotrophin releasing factor (CRF) in the amagdala during the acute withdrawal²⁷. CRF antagonists decrease cocaine self-administration, drug withdrawal and stress-induced re-instatement to opioid, alcohol and cocaine seeking behaviour in rats^{28,29}. Gluco-corticoid receptor antagonists decrease reinforcing properties of stimulants³⁰.

Reinstatement (conditioned relapse) paradigm: Dopaminergic and glutamatergic alterations

In laboratory animals, after extinction of compulsive drug administration, 3 reinstatement paradigms (conditioned cues, drug priming, and stress) are examined, all able to rapidly reinstate drugseeking behaviour or relapse to a previously established addicted state³¹. The afferent dopaminergic projections from ventral tegmental area to prefrontal cortex (mesocortical) and to the amagdala (mesolimbic) are necessary in reinstatement process because drugseeking behaviour (initiated by 3 reinstatement conditions) can be inhibited by activation of ventral tegmental area³²⁻³⁴.

I-RISA Syndrome of Drug Addiction

It encompasses four clusters of behaviours that are interconnected in a positive feed-back loop. These are as follows:

Drug Intoxication: Drug-intoxication is traditionally associated with higher extra-cellular dopamine concentrations in limbic brain regions, in particular, the nucleus accumbens^{35,36}. There is also increased concentration of dopamine in frontal regions³⁷.

Drug Craving: Craving is associated with the learned response of the drug to a pleasurable experience. The neuro-anatomical bases of this memory involve amygdala^{38,39,40} and hippocampus¹⁸.

Activation of thalamo-orbitofrontal circuit and anterior cingulate may be a defining element in the actual experience of craving⁴¹.

Compulsive Drug Administration: Compulsive drug self administration occurs even when the drug is no longer pleasurable and in the presence of adverse physical reactions to the drug⁴².

Loss of control and drug bingeing is associated with dopaminergic, serotonergic, and glutamatergic circuits^{43,44} and involves the activation of the thalamo-orbitofrontal circuit and the anterior cingulate gyrus.

Drug Withdrawal: Drug withdrawal culminates in dysphoria, anhedonia, and irritability [44] contributing to relapse^{45,46}. These changes involve disruption of frontal cortical circuits and neurotransmitters that include dopamine, serotonin, and corticotropin-releasing factor⁴⁷.

INVOLVEMENT OF THE FRONTAL CORTEX

Intoxication: Neuro-imaging studies have assessed the effects of drugs on functional measures, such as glucose metabolism and cerebral blood flow (CBF). Few have measured regional brain activity during drug intoxication with the individual drugs. These studies have shown lower glucose metabolism throughout the brain, including the frontal cortex, during cocaine, morphine, or alcohol intoxication⁴⁸⁻⁵². In marijuana intoxication there are

higher levels of glucose metabolism in the prefrontal cortex, orbito-frontal cortex, and striatum⁵³. Similarly faster metabolism in the prefrontal cortex, anterior cingulate, orbito-frontal cortex, and striatum has been reported in cocaine abusers after sequential administration of intravenous methylphenidate¹⁹. Higher levels of prefrontal CBF during intoxication with nicotine⁵⁴, marijuana⁵⁵, and alcohol⁵⁶⁻⁵⁷ are consistently observed. Activation of the right prefrontal cortex during alcohol intoxication was associated with euphoria⁵⁸ and also with marijuana⁵⁹. In contrast, cocaine lowered CBF throughout the brain, including the frontal cortex perhaps due to vasoconstricting effects⁶⁰. Mapping during drug intoxication with functional magnetic resonance imaging (fMRI) to measure the bloodoxygenation-level-dependent (BOLD) response have reported activation of the prefrontal cortex and anterior cingulate gyrus during cocaine intoxication, an effect that has been strongly correlated with drug reinforcement properties⁶¹. Nicotine administration has also shown activation in the frontal cortex and anterior cingulate gyrus coinciding in time with the subjective experiences of "rush" and "high"⁶².

Craving and Bingeing: Acute drug administration is not necessary for the activation of the frontal cortex in individuals previously exposed to the drug of choice, in whom because of prior exposure, craving alone is possibly sufficient to activate fronto-limbic circuits.

Thus, higher levels of brain activation (CBF, glucose metabolism, or BOLD) in fronto-limbic areas, primarily in the prefrontal cortex and anterior cingulate, has been demonstrated in cocaine abusers exposed to drug related stimuli⁶³⁻⁶⁷. Self-reports of craving is correlated with glucose metabolism changes in the dorsolateral prefrontal cortex⁶⁵ and also with the spatial extent of activation in the dorso-lateral prefrontal cortex and anterior cingulate. The mechanism that underlies craving may entail recall of emotionally laden previous experiences. Craving is associated with activation of the amygdala, and orbito-frontal cortex⁶⁶. The actual drug experience may be related with more circumscribed activations than the anticipation phase⁴², in line with evidence for a similar dissociation of anticipation from an actual sensory (tactile) experience⁴⁶. The role of the frontal cortex in craving is also found. Higher regional brain glucose metabolism, including in the orbito-frontal cortex and striatum, in cocaine abusers during early withdrawal (<1 week since last cocaine use) has been demonstrated⁶⁷. A central role for craving in orbito-frontal cortex activation has also been suggested in a study in which methylphenidate increased orbito-frontal cortex and striatal metabolism only in the subjects in whom it enhanced craving¹⁹.

The cocaine craving is not a direct measure of compulsive cocaine use, and, in fact, its association with drug use and relapse continues to be challenged.⁶⁸

WITHDRAWAL

During cocaine withdrawal in regular cocaine abusers, abnormalities in the cortex were first documented in 1988⁶⁹ that the relative CBF values for the prefrontal cortex and the left lateral frontal cortex were significantly lower in the cocaine users. Differences were found in active cocaine abusers in regional brain glucose metabolism tested within 1 week of last cocaine use and cocaine abusers tested 2-4 weeks after last cocaine use⁶⁷. During prolonged withdrawal (1-6 weeks since last use), brain metabolism was found to be lower in cocaine abusers than in normal comparison subjects, an effect that was most accentuated in the frontal cortex⁷⁰. Glucose metabolism abnormalities (including in the frontal cortex) were documented in otherwise healthy alcoholic subjects with mean duration of alcohol withdrawal of 11 days⁷¹. Persistent lower striatal metabolism has been shown in regional metabolism studies after more protracted alcohol withdrawal⁷². In addition, alcoholic subjects have shown less sensitivity to the lower metabolism induced by lorazepam, a benzodiazepine that facilitates $\bar{\alpha}$ -aminobutyric acid neurotransmission in the striatal-thalamo-orbito-frontal cortex circuit during early (1-4 weeks) detoxification⁷³ and in the orbito-frontal cortex during protracted (8-11 weeks) detoxification⁷⁴, suggesting long-lasting drug-related adjustments in these brain regions. Persistent abnormalities after alcohol detoxification were also documented for the anterior cingulate. Lower activity in the prefrontal cortex in alcoholic subjects during detoxification

was also documented⁷⁵.

Alcoholics show less sensitivity in the striatal-thalamo-orbito-frontal cortex circuit to the serotonin agonist *m*-chlorophenylpiperazine, which provides evidence for the relevance of serotonin in these abnormalities⁶⁹. In cocaine abusers during early (up to 1 month since last cocaine use) and protracted (up to 4 months since last cocaine use) withdrawal, striatal dopamine response or receptor availability was significantly lower^{4,77,78} than in normal comparison subjects. Lower striatal dopamine D2 receptor binding in heroin is also reported⁷⁹ and methamphetamine⁸⁰ abusers and in alcoholic subjects⁸¹. Moreover, the lower levels of striatal D2 receptors were found to be associated with lower metabolism in the orbito-frontal cortex and anterior cingulate gyrus in cocaine addicted subjects⁵⁸ and in the orbito-frontal cortex in methamphetamine abusers⁸².

Finally, higher metabolism in the anterior cingulate gyrus has been shown in response to methylphenidate, which increases dopamine by blocking the dopamine transporter¹⁹, providing further support for the role of lower dopamine activation in frontal hypometabolism in drug addiction.

I-RISA Syndrome and Dopamine circuits: The mesolimbic and the mesocortical dopamine systems are classically associated with drug reinforcement and addiction. The mesolimbic dopamine circuit, which includes the nucleus accumbens, amygdala, and hippocampus, has been traditionally associated with the acute reinforcing effects of a drug and with the memory and conditioned responses that have been linked to craving. Involved in the emotional and motivational changes seen in drug abusers during withdrawal is also there⁸³. The mesocortical dopamine circuit, which includes the prefrontal cortex, orbito-frontal cortex, and anterior cingulate, is likely to be involved in the conscious experience of drug intoxication, drug incentive salience, drug expectation/craving, and compulsive drug administration. Because these circuits operate in parallel and interact with one another, it is likely that a given behavior involves, to a greater or lesser extent, their joint participation. For example, the activation of memory circuits (the hippocampus and amygdala) in association with a drug-related context activates the orbitofrontal cortex and anterior cingulate in expectation of the reinforcer, which in turn activates the dopamine cells⁸⁴, leading to a further increase in the craving sensation and a possible decrease in inhibitory control. There is the circular nature of this interaction: the attribution of salience to a given stimulus, which is a function of the orbito-frontal cortex, depends on the relative value of a reinforcer compared to simultaneously available reinforcers⁸⁵, which require knowledge of the strength of the stimulus as a reinforcer, a function of the hippocampus and amygdala. Consumption of the drug in turn will further activate cortical circuits (the orbito-frontal cortex and anterior cingulate) in proportion to the dopamine stimulation by favoring the target response and decreasing nontarget-related background activity⁸⁶. The activation of these interacting circuits may be indispensable for maintaining the compulsive drug administration observed during bingeing and to the vicious circle of drug addiction.

The neurobiological mechanisms of why some particular individuals become addicts and others do not, is poorly understood. The underlying vulnerability to drug addiction is likely to involve a balance between factors that confer vulnerability and those that protect against it. It is hypothesized that the decrease in activity of D2 receptors may put individuals at risk for addictive behaviors as a means of temporarily compensating for the fewer D2-regulated reward circuits⁸⁷. This is also seen that over-expression of D2 receptors in the nucleus accumbens of rats previously trained to self-administer alcohol markedly reduces their alcohol intake⁸⁸. Since D2 receptor availability is positively associated with frontal activity in the human brain, this suggests that one of the mechanisms by which D2 receptors regulate drug self-administration, and possibly the potential for addiction, is by modulating frontal activity.

Neurocognitive Mechanisms: The functional neuroimaging studies conducted in healthy comparison subjects or non-drug-abusing populations have implicated the striatal-thalamo-orbito-frontal cortex circuit in the I-RISA components. The four components can be viewed as intricately related to the four dimensions of drug-addiction model each potentially predisposing to

drug addiction:

1. Drug intoxication is associated with the experience of its strong positive and negative reinforcement effects, an association that is strengthened through repeated self-administration and that possibly hinders the formation of similar associations; attribution of primary salience to the drug occurs at the expense of less powerful reinforcers.
2. Impairment in response inhibition is conceived as underlying the experience of relapse and bingeing. When response reinforcement regulation is down because of impaired salience attribution, response disinhibition, or impulsive responding to immediately salient, drug-related rewards is expected.
3. Expectation of the effects of the drug of abuse, whether it is the "high" or a lower negative state, is integral to drug craving.
4. Dysthymia is a core symptom of withdrawal, possibly reflecting adaptation responses to repeated dopamine enhancement by drugs of abuse in the reward circuits that render the latter less responsive to natural reinforcers⁸⁹⁻⁹². Behaviorally, this lower sensitivity in the reward circuits may represent a generalized impairment in the ability to derive pleasure from non-drug-related stimuli, leading to a state of anhedonia, which puts drug-addicted individuals at greater risk for seeking drug stimulation

Reinforcement relations and salience attribution response: Regarding perception of response-reinforcement relations, several recent fMRI studies have monitored brain hemodynamic changes during performance of game-playing tasks with monetary reinforcers.

Responses to monetary gains and losses or to winning and losing game points have been noted in the prefrontal cortex, orbito-frontal cortex, anterior cingulate, and thalamus. Activations of these areas in guessing, compared to reporting (the orbito-frontal cortex was exclusively activated in the guessing task in the more difficult condition, in which probability of being correct was down to 25% from 50%), point to a unique role of the correctness of a response and greater dependence on feedback under conditions of inherent uncertainty^{93,94}. A fMRI study documented that unpredictability of a reward (water or juice) correlated with activity in the orbitofrontal cortex, thalamus, and nucleus accumbens⁹⁵. PET studies have demonstrated striatal-thalamo-orbito-frontal cortex activations (including the anterior cingulate and dorsolateral prefrontal cortex) in association with gambling^{96,97}, receiving a salient feedback⁹⁸, or receiving a monetary reward⁹⁹. The processing of emotionally salient and behaviorally adaptive information may be at the core of advantageous assessment of response-reinforcement relations. The role of the frontal cortex, and specifically the anterior cingulate, in emotional processing has been demonstrated in several PET studies¹⁰⁰⁻¹⁰⁶ and the orbito-frontal cortex in recognizing fearful, angry, and disgusted emotional facial expressions compared to neutral expressions¹⁰⁶. Of interest, in a PET study¹⁰⁷, angry but not sad faces specifically activated the orbito-frontal cortex, proportionally with the increasing intensity of the emotion, while the anterior cingulate cortex was co-activated by both expressions.

Taken together, the results of these studies suggest an important integrative role for the orbito-frontal cortex and anterior cingulate in the analysis of the information that carries emotive, evaluative, and, in the long-term, survival significance for an individual, which comprise salience attribution, an integral part of I-RISA syndrome of drug addiction.

RESPONSE INHIBITION

The other component of the proposed I-RISA syndrome is the control of behavior, which is assumed to break down in periods of relapse and drug bingeing. Response inhibition has been relatively well studied in neuroimaging paradigms. The orbito-frontal cortex, anterior cingulate cortex, and striatum were activated in a go/no go task in two fMRI studies^{108,109}. Better response inhibition was associated with greater volume of activation in the orbito-frontal cortex and a smaller magnitude of activation in the anterior cingulate cortex, possibly implicating the orbitofrontal cortex in the effort exerted when inhibiting a response and the anterior cingulate cortex in error detection¹⁰⁸. Further support for the role of the anterior cingulate in response

inhibition, including response competition and selection, is provided by other fMRI^{104,110-114} and PET studies of the go/no-go paradigm. In addition, the role of the anterior cingulate in response inhibition has been established in studies of the suppression of prepotent response tendencies by using the Stroop effect. More direct evidence for the role of the prefrontal circuit in response inhibition in drug addiction¹¹⁵. We examined the association between Stroop interference and relative glucose metabolism in selected prefrontal brain regions in cocaine-addicted subjects, alcoholic subjects, and comparison subjects. The results revealed that for the cocaine-addicted subjects and alcoholic subjects, higher levels of orbito-frontal cortex metabolism at baseline was associated with lower conflict (higher Stroop interference score), while for the comparison subjects, higher orbito-frontal cortex metabolism was associated with higher conflict (lower Stroop interference score), suggesting a change in the role of the orbitofrontal cortex as a function of addiction.

Expectation: Supporting the role of the frontal cortex in expectation is an fMRI study that demonstrated distinct brain regions and different response characteristics in anticipation of pain versus the experience of pain, with the former activating more anterior regions (including the anterior medial frontal cortex) than the latter⁴⁶. Activation of the orbito-frontal cortex has also been associated with expectation in several PET studies, including expectation in tasks of visual attention¹⁰⁶ and in tasks involving a shock^{107, 108}.

Dysthymia: Finally, an association between depression and prefrontal abnormalities has been demonstrated in neuroimaging studies conducted in depressed patients, with suggested disruptions of fronto-striatal¹⁰⁹ and cortico-limbic¹⁰⁰ networks. Results of these studies revealed resting abnormalities in the dorsolateral, ventrolateral, and medial aspects of the prefrontal cortex and the anterior cingulate, blunted responses in the anterior cingulate and medial prefrontal cortex to behavioral and pharmacological challenges, and abnormalities localized to the orbito-frontal cortex^{110,111}. Lower activity in the striatum of depressed patients in the resting state and in response to a reaction-time task and feedback have also been reported^{112,113}.

With the increasing evidence, the neurobiology of addiction disorders has become clearer. Such characterization not only provides a greater understanding of why people become addicted and what happens to the brain after a period of substance misuse, but also allows better understanding of current pharmacotherapies and the development of new treatments.

REFERENCES

1. Jiloha RC. Biological basis of tobacco addiction: Implications for smoking-cessation treatment. *Indian J Psychiatry*;5(2):301-307.
2. Ross Stephen. Neurobiology of addictive behaviour. *Clinical Neuropharmacology*. 2009;32(5):270-274.
3. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology*;2008;33:166-180.
4. Jiloha RC. Management of lapse and relapse in drug dependence. *Delhi Psychiatry Journal*;2011;14(2):199-204.
5. Volkow ND. Cocaine cues and dopamine dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci*;2006;26:6583-6588.
6. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry*. 2005;162:1403-1411.
7. Polas MP. Neural basis of reward and craving – a homeostatic point of view. *Dialogues Clin Neurosci*;2007;9:379-387.
8. Koob, G. F. & Le Moal, M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*;2001;24:97-124
9. Volkow, N. D., Fowler, J. S. & Wang, G. J. Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. *Journal of Psychopharmacology*. 1999;13: 337-345.
10. Schultz, W. Reward signaling by dopamine neurons. *Neuroscientist*. 2001; 7:293-302.
11. Nutt, D. & Malizia, A. L. New insights into the role of the GABA—benzodiazepine receptor in psychiatric disorder. *British Journal of Psychiatry*. 2001; 179: 390-396.
12. Pilla, M., Perachon, S., Sautel, F. Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist. *Nature*. 1999; 400: 371-375.
13. Jorenby, D. E., Leischow, S. J., Nides, M. A. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine*. 1999;340:685-691.
14. Ascher, J. A., Cole, J. O., Colin, J. NBupropion: a review of its mechanism of antidepressant activity. *Journal of Clinical Psychiatry*. 1995;56: 395-401.
15. Hyman SE. Addiction: a disease of learning and memory. *Am J Psychiatry*;2005;162:1414-1422.
16. Baler RD, Volkow ND. Drug addiction: the neurobiology of disrupted self-control. *Trends Mol Med*. 2006;12(12):559-566.
17. Koob GF. Neurobiology of addiction. In: Galanter M, Kleber HD. Eds. *Text Book of Substance Abuse Treatment*. 4th Ed. Arlington VA. American Psychiatric Publishing, Inc; 2008:3-16.
18. Kalivas PW. Neurotransmission regulation of dopamine neurons in the ventral tegmental area. *Brain Res Rev*. 1993; 18(1):75-113.
19. Heidebreder C. Neuropharmacological targets for the management of drug addiction. *Eur J Pharmacol*;2005;526:101-112.
20. Wise RA. Brain reward circuitry: insights from unsensed incentives. In: Graham AW, Schultz TK, Mayo-Smith MF. *Principles of Addiction Medicine*. 3rd Ed. Chevy Chase MD. American Society of Addiction Medicine, Inc. 3003:57-71.
21. Grant JE, Brewer JA, Potenza MN. The neurobiology of substance and behaviour addictions. *CNS Spectr*;2006;11(9):924-930.
22. Wlaskh SL, Cunningham KA. Serotonergic mechanism involved in the discriminative stimulus, reinforcing and subjective effects of cocaine. *Psychopharmacology*;1997;130:41-58.
23. Krystal JH. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: towards a paradigm

- shift in medication development. *Psychopharmacology* 2003;169:215-233.
24. **Harvitz JC.** Mesolimbic and nigrostriatal dopamine responses to salient non-reward events. *Neuroscience* 2000;96:651-656.
 25. **Schultz W, Dayan P and Montague PR.** A neural substrate of prediction and reward. *Science* 1997;275:1593-1599.
 26. **Kalivas PW.** Cocaine and amphetamine-like psychostimulants: neurocircuitry and glutamate neuroplasticity. *Dialogues Clin Neurosci* 2007;9:389-379.
 27. **Weiss F.** Compulsive drug-seeking behaviour and relapse. *Neuro-adaptation, stress and conditioning factors.* *Ann N Y Acad Sci* 2001;937:1-26.
 28. **Nie Z.** Ethanol augments GABAergic transmission in the central amygdala via CRF1 receptors. *Science* 2004; 303:1512-1514
 29. **Shaham Y.** CP-154, 526, a selective non-peptide antagonist of corticotrophin-releasing factor 1 receptor attenuates stress induced relapse to drug-seeking cocaine- and heroin trained rats. *Psychopharmacology* 1998; 137: 184-190.
 30. **Deroche-Gamonet.** The glutamate receptor as a potential target to reduce cocaine abuse. *J Neurosci.* 2003;23:4785-4790.
 31. **Shaham Y.** The reinstatement model of drug-relapse: history, methodology and major findings. *Psychopharmacology* 2003; 168:3-20.
 32. **McFarland K.** Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine seeking behaviour. *J Neurosci* 2004;24:1551-1560.
 33. **McFarland K, Kalivas PW.** The circuitry mediated cocaine-induced reinstatement of drug-seeking behaviour. *J Neurosci.* 2001;21:8656-8663.
 34. **DiCiano P, Everitt BJ.** Contribution of ventral tegmental area cocaine seeking maintained by a drug-paired conditioned stimulus in rats. *Eur J Neurosci.* 2004;19:1661-1667.
 35. **Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ.** Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* 1987; 237:1219-1223
 36. **Hurd YL, Ungerstedt U.** Cocaine: an in vivo microdialysis evaluation of its acute action on dopamine transmission in rat striatum. *Synapse* 1989; 3:48-54
 37. **Goeders NE, Smith JE.** Reinforcing properties of cocaine in the medial prefrontal cortex: primary action on presynaptic dopaminergic terminals. *Pharmacol Biochem Behav* 1986; 25: 191-199
 38. **Brown EE, Fibiger HC.** Differential effects of excitotoxic lesions of the amygdala on cocaine-induced conditioned locomotion and conditioned place preference. *Psychopharmacology (Berl)* 1993; 113:123-130
 39. **Meil WM, See RF.** Lesions of the basolateral amygdala abolish the ability of drug-associated cues to reinstate responding during withdrawal from self-administered cocaine. *Behav Brain Res* 1997; 87:139-148
 40. **Franklin TR, Druhan JP.** Expression of Fos-related antigens in the nucleus accumbens and associated regions following exposure to a cocaine-paired environment. *Eur J Neurosci* 2000; 12:2097-2106
 41. **Volkow ND, Wang G-J, Fowler JS, Hitzemann R, Angrist B, Gatley SJ, Logan J, Ding Y-S, Pappas N.** Association of methamphetamine-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. *Am J Psychiatry* 1999; 156:19-26
 42. **Fischman MW, Schuster CR, Javadi J, Hatan Y, Davis J.** Acute tolerance development to the cardiovascular and subjective effects of cocaine. *J Pharmacol Exp Ther* 1985; 235:677-682
 43. **Loh EA, Roberts DC.** Break-points on a progressive ratio schedule reinforced by intravenous cocaine increase following depletion of forebrain serotonin. *Psychopharmacology (Berl)* 1990; 101:262-266
 44. **Cornish JL, Duffy P, Kalivas PW.** A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behavior. *Neuroscience* 1999; 93:1359-1367
 45. **Wilner F, Muscat R, Papp M.** Chronic mild stress-induced anhedonia: a realistic animal model of depression. *Neurosci Biobehav Rev* 1992; 16:525-534
 46. **Hodgins DC, el-Guebaly N, Armstrong S.** Prospective and retrospective reports of mood states before relapse to substance use. *J Consult Clin Psychol* 1995; 63:400-407
 47. **Johnson CE, Fischman MW.** The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989; 41:3-52
 48. **Koob GF, Le Moal M.** Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 2001; 24:97-129
 49. **Volkow ND, Hitzemann R, Wolf AP, Logan J, Fowler JS, Christian D, Dewey SL, Schlyer D, Burr G, Vitkun S, Herschowitz J.** Acute effects of ethanol on regional brain glucose metabolism and transport. *Psychiatry Res* 1990; 35:39-48
 50. **London ED, Brousselle EPM, Links JM, Wong DF, Cascella NG, Dannals RF, Sano M, Herning R, Snyder FR, Rippele LR, Toung TJK, Jaffe JH, Wagner HN Jr.** Morphine-induced metabolic changes in human brain: studies with positron emission tomography and [¹⁸F]fluorodeoxyglucose. *Arch Gen Psychiatry* 1990; 47:73-81
 51. **London ED, Cascella NG, Wong DF, Phillips RL, Dannals RF, Links JM, Herning R, Grayson R, Jaffe JH, Wagner HN Jr.** Cocaine-induced reduction of glucose utilization in human brain: a study using positron emission tomography and [¹⁸F]fluorodeoxyglucose. *Arch Gen Psychiatry* 1990; 47:567-574
 52. **de Wit H, Metz J, Wagner N, Cooper M.** Behavioral and subjective effects of ethanol: relationship to cerebral metabolism using PET. *Alcohol Clin Exp Res* 1990; 14:482-48
 53. **Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, Hollister L.** Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. *Psychiatry Res* 1996; 67:29-38
 54. **Nakamura H, Tanaka A, Nomoto Y, Ueno Y, Nakayama Y.** Activation of fronto-limbic system in the human brain by cigarette smoking: evaluated by a CBF measurement. *Keio J Med* 2000; 49(suppl 1):A122-A124
 55. **Mathew RJ, Wilson WH, Humphreys DF, Lowe JV, Wiethe KE.** Regional cerebral blood flow after marijuana smoking. *J Cereb Blood Flow Metab* 1992; 12:750-758.
 56. **Volkow ND, Mullani N, Gould L, Adler SS, Gaynor RW, Overall JE, Dewey S.** Effects of acute alcohol intoxication on cerebral blood flow measured with PET. *Psychiatry Res* 1988; 24:201-209.
 57. **Tiihonen J, Kuikka J, Hakola P, Paanila J, Atrakainen J, Eronen M, Hallikainen T.** Acute ethanol-induced changes in cerebral blood flow. *Am J Psychiatry* 1994; 151:1505-1508 Ingvar M, Ghatan PH, Wirsén-Meurling A, Risberg J, Von Heijne G, Stone-Elinder S, Ingvar DH: Alcohol activates the cerebral reward system in man. *J Stud Alcohol* 1998; 59:258-269.
 58. **Wallace EA, Wisniewski G, Zubal G, van Dyck CH, Pfau SE, Smith EO, Rosen MI, Sullivan MC, Woods SW, Kosten TR.** Acute cocaine effects on absolute cerebral blood flow. *Psychopharmacology (Berl)* 1996; 128:17-20.
 59. **Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JR, Mathew RT, Rosen BR, Hyman SE.** Acute effects of cocaine on human brain activity and emotion. *Neuron* 1997; 19:591-611.
 60. **Sein EA, Pankiewicz J, Harsch HH, Cho J-K, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS.** Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. *Am J Psychiatry* 1998; 155:1009-1015.
 61. **Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP.** Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 1999; 156:11-18.
 62. **Garavan H, Pankiewicz J, Bloom A, Cho J-K, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA.** Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry* 2000; 157:1789-1798.
 63. **Grant S, London ED, Newlin DB, Villmagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A.** Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci USA* 1996; 93:12040-12045.
 64. **Maas LC, Lukas SE, Kaufman MJ, Weiss RD, Daniels SL, Rogers VW, Kukes TJ, Renshaw PF.** Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *Am J Psychiatry* 1998; 155:124-126.
 65. **Wexler BE, Gottschalk CH, Fulbright RK, Prohovnik I, Lacadie CM, Rounsaville BJ, Gore JC.** Functional magnetic resonance imaging of cocaine craving. *Am J Psychiatry* 2001; 158:86-95.
 66. **Wang G-J, Volkow ND, Fowler JS, Cervany P, Hitzemann RJ, Pappas NR, Wong CT, Felder C.** Regional brain metabolic activation during craving elicited by recall of previous drug experiences. *Life Sci* 1999; 64:775-784.
 67. **Ploghaus A, Tracey J, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN.** Dissociating pain from its anticipation in the human brain. *Science* 1999; 284:1979-1981.
 68. **Volkow ND, Fowler JS, Wolf AP, Hitzemann R, Dewey S, Bendriem B, Alpert R, Hoff A.** Changes in brain glucose metabolism in cocaine dependence and withdrawal. *Am J Psychiatry* 1991; 148:621-626.
 69. **Tiffany ST.** A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychol Rev* 1990; 97:147-168.
 70. **Volkow ND, Mullani N, Gould KL, Adler S, Krajewski K.** Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. *Br J Psychiatry* 1988; 152:641-648.
 71. **Volkow ND, Hitzemann R, Wang G-J, Fowler JS, Wolf AP, Dewey SL, Handelman L.** Long-term frontal brain metabolic changes in cocaine abusers. *Synapse* 1992; 11:184-190.
 72. **Volkow ND, Hitzemann R, Wang G-J, Fowler JS, Burr G, Pascani K, Dewey SL, Wolf AP.** Decreased brain metabolism in neurologically intact healthy alcoholics. *Am J Psychiatry* 1993; 150:1016-1022
 73. **Volkow ND, Wang G-J, Hitzemann R, Fowler JS, Overall JE, Burr G, Wolf AP.** Recovery of brain glucose metabolism in detoxified alcoholics. *Am J Psychiatry* 1994; 151:178-183.
 74. **Volkow ND, Wang G-J, Hitzemann R, Fowler JS, Wolf AP, Pappas N, Biegon A, Dewey SL.** Decreased cerebral response to inhibitory neurotransmission in alcoholics. *Am J Psychiatry* 1993; 150:417-422.
 75. **Volkow ND, Wang G-J, Overall JE, Hitzemann R, Fowler JS, Pappas N, Fresca E, Piscani K.** Regional brain metabolic response to lorazepam in alcoholics during early and late alcohol detoxification. *Alcohol Clin Exp Res* 1997; 21:1278-1284.
 76. **Catafau AM, Etcheberrigaray A, Perez de los Cobos J, Estorch M, Guardia J, Flotats A, Berna L, Mari C, Casas M, Carrio I.** Regional cerebral blood flow changes in chronic alcoholic patients induced by naltrexone challenge during detoxification. *J Nucl Med* 1999; 40:19-24.
 77. **Hommer D, Andreasen P, Rio D, Williams W, Rutimann A, Momen R, Zamekin A, Rawlings R, Linnola M.** Effects of methylphenylpiperazine on regional brain glucose utilization: a positron emission tomographic comparison of alcoholic and control subjects. *J Neurosci* 1997; 17:2796-2806.
 78. **Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shue C-Y, Alpert R, Dewey SL, Logan J, Bendriem B, Christian D, Hitzemann R, Henn F.** Effects of chronic cocaine abuse on postsynaptic dopamine receptors. *Am J Psychiatry* 1990; 147:719-724.
 79. **Volkow ND, Fowler JS, Wang G-J, Hitzemann R, Logan J, Schlyer D, Dewey S, Wolf AP.** Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* 1993; 14:169-17.
 80. **Wang GJ, Volkow ND, Fowler JS, Logan J, Abumrad NN, Hitzemann RJ, Pappas NS, Pascani K.** Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. *Neuropsychopharmacology* 1997; 16:174-182.
 81. **60. Volkow ND, Chang L, Wang G-J, Fowler JS, Leonido-Yee M, Franceschi D, Sedler MJ, Gatley SJ, Hitzemann R, Ding Y-S, Logan J, Wang C, Miller EN.** Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry* 2001; 158:377-382.
 82. **Volkow ND, Wang G-J, Fowler JS, Logan J, Hitzemann R, Ding Y-S, Pappas N, Shea C, Piscani K.** Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcohol Clin Exp Res* 1996; 20:1594-1598
 83. **Volkow ND, Chang L, Wang G-J, Fowler JS, Ding Y-S, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N.** Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry* 2001; 158:2015-2021
 84. **Jentsch JD, Taylor JR.** Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)* 1999; 146:373-390
 85. **Karremans M, Moghaddam B.** The prefrontal cortex regulates
 86. **the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area.** *J Neurochem* 1996; 66:b589-598
 87. **Schultz W, Tremblay L, Hollerman JR.** Reward processing in primate orbitofrontal cortex and basal ganglia. *Cereb Cortex* 2000; 10:272-284
 88. **Kiyatkin EA, Rebec GV.** Dopaminergic modulation of glutamate-induced excitations of neurons in the neostriatum and nucleus accumbens of awake, unrestrained rats. *J Neurophysiol* 1996; 75:142-153
 89. **Volkow ND, Wang G-J, Fowler JS, Logan J, Gatley SJ, Gifford A, Hitzemann R, Ding Y-S, Pappas N.** Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *Am J Psychiatry* 1999; 156:1440-1445
 90. **Thanos PK, Volkow ND, Freimuth P, Umegaki H, Ikari H, Roth G, Ingram DK, Hitzemann R.** Overexpression of dopamine D2 receptors reduces alcohol self-administration. *J Neurochem* 2001; 78:1094-1103
 91. **Volkow ND, Fowler JS.** Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex* 2000; 10:318 Cassens G, Actor C, Kling M, Schildkraut JI: Amphetamine withdrawal: effects on threshold of intracranial reinforcement. *Psychopharmacology (Berl)* 1981; 73:318-322
 92. **Barr AM, Phillips AG.** Withdrawal following repeated exposure to d-amphetamine decreases responding for a sucrose solution as measured by a progressive ratio schedule of reinforcement. *Psychopharmacology (Berl)* 1999; 141:99-106
 93. **Barr AM, Fiorino DF, Phillips AG.** Effects of withdrawal from an escalating dose schedule of d-amphetamine on sexual behavior in the male rat. *Pharmacol Biochem Behav* 1999; 64:597-604
 94. **Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P.** Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron* 2001; 30:619-639
 95. **Elliott R, Rees G, Dolan RJ.** Ventromedial prefrontal cortex mediates guessing. *Neuropsychologia* 1999; 37:403-411
 96. **Berns GS, McClure SM, Pagnoni G, Montague PR.** Predictability modulates human brain response to reward. *J Neurosci* 2001; 21:2793-2798
 97. **Grant SJ, Bonson KR, Contoreggi CC, London ED.** Activation of the ventromedial prefrontal cortex correlates with gambling task performance: a FDG-PET study. *Abstracts of the Society for Neuroscience* 1999; 25(part 2):1551
 98. **Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, Robbins TW.** Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J Neurosci* 1999; 19:9029-9038
 99. **Elliott R, Frieh CD, Dolan RJ.** Differential neural response to positive and negative feedback in planning and guessing tasks. *Neuropsychologia* 1997; 35:1395-1404
 100. **Thut G, Schulte W, Roelcke U, Nienhusmeier M, Missimer J, Maguire RP, Leenders KL.** Activation of the human brain by monetary reward. *Neuroreport* 1997; 8:1225-1228
 101. **George MS, Ketter TA, Gill DS, Haxby JV, Ungerleider LG, Herscovitch P, Post RM.** Brain regions involved in recognizing facial emotion or identity: an oxygen-15 PET study. *J Neurosurg Clin Neurosci* 1993; 5:384-394
 102. **Lane RD, Fink GR, Chau PM, Dolan RJ.** Neural activation during selective attention to subjective emotional responses. *Neuroreport* 1997; 8:3969-397
 103. **Pardo JV, Pardo PJ, Raichle ME.** Neural correlates of self-induced dysphoria. *Am J Psychiatry* 1993; 150:713-719
 104. **Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC.** Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997; 277:968-971
 105. **Elliott R, Rubinstein JS, Sahakian BJ, Dolan RJ.** Selective attention to emotional stimuli in a verbal go/no-go task: an fMRI study. *Neuroreport* 2000; 11:1739-1744
 106. **Francis S, Rolls ET, Bowtell R, McGlone F, O'Doherty J, Browning A, Clare S, Smith E.** The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. *Neuroreport* 1999; 10:453-459
 107. **Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H.** Neural structures associated with recognition of facial expressions of basic emotions. *Proc R Soc Lond B Biol Sci* 1998; 265:1927-1931
 108. **Blair RJR, Morris JS, Frith CD, Perrett DI, Dolan RJ.** Dissociable neural responses to facial expressions of sadness and anger. *Brain* 1999; 122:883-893
 109. **Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Gidd JN, Castellanos FX, Huxley JV, Noll DC, Cohen JD, Forman SD, Dahl RE, Rapoport JL.** A developmental functional MRI study of prefrontal activation during performance of a go-no-go task. *J Cogn Neurosci* 1997; 9:835-847
 110. **Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, Gabrieli JDE.** Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc Natl Acad Sci USA* 1998; 95:14494-14499
 111. **Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD.** Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 1998; 280:747-749
 112. **Kiehl KA, Liddle PF, Hopfinger JB.** Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology* 2000; 37:216-223
 113. **Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SCR, Simmons A, Andrew C, Bullmore ET.** Functional frontalization with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci Biobehav Rev* 2000; 24:13-19
 114. **Krams M, Rushworth MFS, Deiber MP, Frackowiak RJ, Passingham RE.** The preparation, execution and suppression of copied movements in the human brain. *Exp Brain Res* 1998; 120:386-398
 115. **Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, Cohen JD.** Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proc Natl Acad Sci USA* 2000; 97:1944-1948