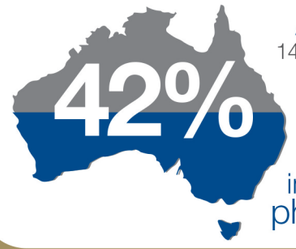
# N-acetyl-cysteine (NAC): addictions, compulsions and impulsive behaviours

FX Medicine

**ADDICTION**
**IS A DISEASE**
NOT a personality disorder[1]




AUSTRALIANS
14 years or older had used
**ILLICIT DRUGS**
including misuse of pharmaceuticals[2]

The most **common** drugs people seek **treatment** for are:[3]
- Alcohol (46%)
- Cannabis (22%)
- Amphetamines (11%)
- Heroin (9%)

Alcohol and other drugs cost Australian workplaces
**$6 BILLION**
per year in lost productivity[4]

## WHAT IS NAC?[5,6]

N-acetyl-cysteine is a precursor to the amino acid L-cysteine. NAC plays a key role in managing oxidative stress as the rate-limiting component in the synthesis of the endogenous antioxidant glutathione (GSH). In addition to its role as an antioxidant, NAC also acts as a modulator of the glutamatergic system, which is related to reward-seeking repetitive behaviours, and may contribute to psychiatric syndromes characterised by impulsive and compulsive behaviours.

## WHAT IS ADDICTION?[5,7]

Addiction is repeated involvement with a substance or activity, despite the substantial harm it causes, because that involvement was (and may continue to be) pleasurable and/or valuable.

## TYPES OF ADDICTION[5-7]

**SUBSTANCE-RELATED ADDICTIONS**

- Alcohol
- Cannabis
- Hallucinogens
- Inhalants
- Opioids
- Sedatives, hypnotics or anxiolytics
- Stimulants
- Tobacco

**BEHAVIOURAL ADDICTIONS**

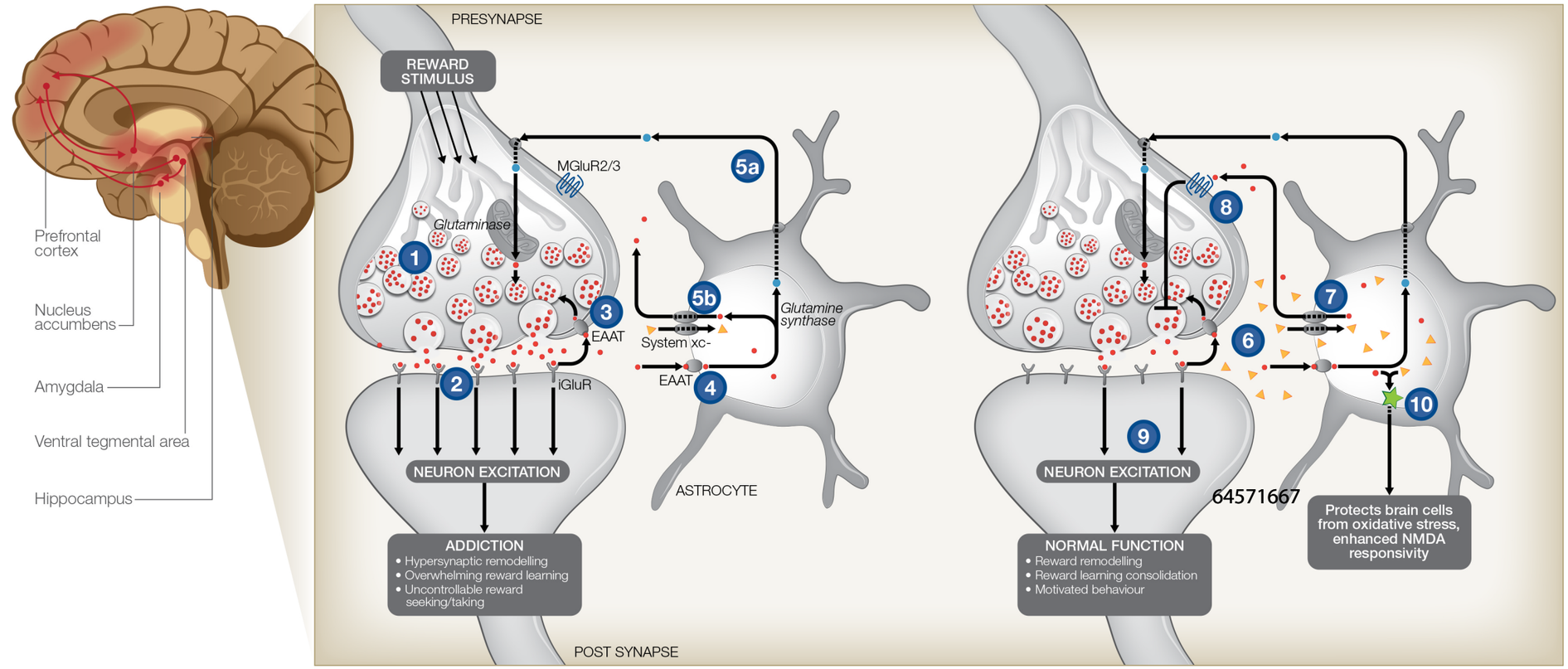
- Gambling
- Sex/pornography
- Eating disorders
- Trichotillomania (hair pulling)
- Smartphones/internet
- Video games
- Work
- Shopping
- Kleptomania

## SYMPTOMS[7]

- Inability to limit use of a substance or activity beyond need, leading to clinically significant impairment.
- Craving or compulsion to use the substance or activity.
- Tolerance – more frequent use of the drug or activity is required to achieve the desired effect.
- Attempts to stop usage produce symptoms of withdrawal e.g. irritability, anxiety, shakes, nausea.
- Recurrent use of the substance or activity impairs work, social and family responsibilities, creates psychological impairments and interpersonal problems, has negative effects on health, mood, self-respect, exacerbated by the effects of the specific substance itself.

All addictions have the capacity to induce feelings of shame and guilt, a sense of hopelessness and feelings of failure. In addition, anxiety and depression are common conditions among those with substance and behavioural addictions.

## GLUTAMATE PATHWAY – WHAT HAPPENS IN THE BRAIN?[5,8,9]

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| | |
|---|---|
| | Glutamate pathway in the brain |
| | Glutamate |
| | Cysteine |
| | Glutamine |
| | Glutathione (GSH) |
| | Metabotropic glutamate receptors 2/3 (MGluR2/3) |
| iGluR | Ionotropic glutamate receptor |
| EAAT | Excitatory amino acid transporter |
| System xc- | Cystine/glutamate exchanger |

**1.** Glutamate is packaged into presynaptic vesicles.

**2.** Glutamate is released into the synaptic cleft and binds to postsynaptic localised iGluRs e.g. alpha-amino-3-hydroxy-5-methylisoxazole-4 propionic acid (AMPA), N-methyl-D-aspartate (NMDA) and kainate receptors resulting in strengthening of long-term potentiation within the brain reward circuitry and development of addictive behaviours.

**3.** EAATs on the presynaptic terminal take in extracellular glutamate for repacking into vesicles. This protects extrasynaptic receptors from synaptic glutamate and synaptic receptors from extrasynaptic glutamate.

**4.** EAATs on astrocytes uptake glutamate.

**5a.** Glutamate is converted to glutamine via glutamine synthetase and released into the extracellular space where it is taken up by presynaptic transporters, metabolised to glutamate and packaged into vesicles.

**5b.** Glutamate is transported into the extracellular environment by the System xc- in a 1:1 ratio.

**6.** Administration of NAC helps to normalise extracellular glutamate dysregulation by providing cysteine.

**7.** Increased levels of cysteine enhances activation of the System xc-.

**8.** Enhanced activation of System xc- results in increased concentration of glutamate in the extracellular space, which binds to MGluR2/3 leading to **suppression of presynaptic glutamate release**.

**9.** Reduced iGluR activation as a downstream result of NAC administration, **restores capacity for long term potentiation and development of normal function behaviours**.

**10.** Increased intracellular cysteine is combined with intracellular glutamate (and glycine) to synthesise GSH, which is released from the astrocyte into the extracellular space providing the precursors necessary for **neuronal GSH production and oxidative protection as well as direct modulation of glutamatergic stimulation enhanced NMDA responsivity**.