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Treating cue-reactivity with brain stimulation: a new (transdiagnostic) approach

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The struggle between internal self-control and external temptation from environmental cues is a tale as old as written history, yet as relevant today as any time in the past. Just as Homer wrote about Odysseus and the seductive Siren Songs (800 B.C.), or Tintorreto painted Adam's temptation in the Garden of Eden (1551 A.D.), twenty-first century depictions of life frequently highlight the struggle to maintain focus despite proverbial "apples" that interrupt our journey. For most individuals, the occasional surrender to a tempting cue will not impair their ability to fulfill daily and longer term responsibilities. For other individuals, however, elevated reactivity to positive or negative cues causes a disabling cascade of events ultimately impeding long-term goals. Elevated cue-reactivity is also a prominent feature of alcohol and substance-use disorder, posttraumatic stress disorder (PTSD), and obsessive behavior disorders, such as eating and gambling.

In these populations, salient cues evoke elevated activity in a consistent network of neural regions: the ventral medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), and insula. This network may be thought of as a "transdiagnostic neural biomarker" for cue-reactivity. In substance-abuse literature, meta-analyses have demonstrated that these regions are reliably activated by drug cues and may predict relapse [1, 2]. In a recent study by our group, 156 substance dependent individuals performed a drug cue-exposure task tailored to their drug of choice (55 cocaine, 53 alcohol, 48 nicotine) [3]. Multivariate k-means clustering revealed three distinct clusters of elevated activity when the participants were viewing the drug cues vs. neutral non-drug cues: the MPFC/ACC, the left inferior frontal gyrus/insula, and the right premotor cortex.

From a therapeutic perspective, novel non-invasive brain stimulation treatment protocols are being designed to target the MPFC–ACC–Insula circuit directly [4]. In the cue-reactivity study described above, cortical projection analysis revealed that the frontal pole (FP) was the cortical location closest to the maximal number of significant cue-reactivity clusters. A recent sham-controlled study in 49 individuals demonstrated that continuous theta burst stimulation (TBS)—a particularly potent and efficient form of transcranial magnetic stimulation (TMS)—directed to the left FP decreases drug cue-reactivity among heavy alcohol users and cocaine users [5]. This protocol also decreases functional connectivity in this MPFC/ACC/Insula network [6].

FP TMS is also being used to improve cue-reactivity in PTSD and obsessive behavioral disorders. Dr Rebecca Price and colleagues at the University of Pittsburg, e.g., are currently evaluating FP TBS, as a tool to decrease compulsive behaviors in obsessive compulsive disorder, many of which are cue-evoked (NCT #03265015). The use of this MPFC–ACC–Insula network as a framework for modulating cue-reactivity is just beginning. Although there will be several challenges associated with developing TMS strategies to modulate this network (e.g., reaching these deep targets, disease-tailored protocols), the MPFC–ACC–Insula network appears to be a fruitful and transdiagnostic neural biomarker to explore for next generation brain stimulation protocols.

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ADDITIONAL INFORMATION

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Decoding the role of the microbiome on amygdala function and social behaviour

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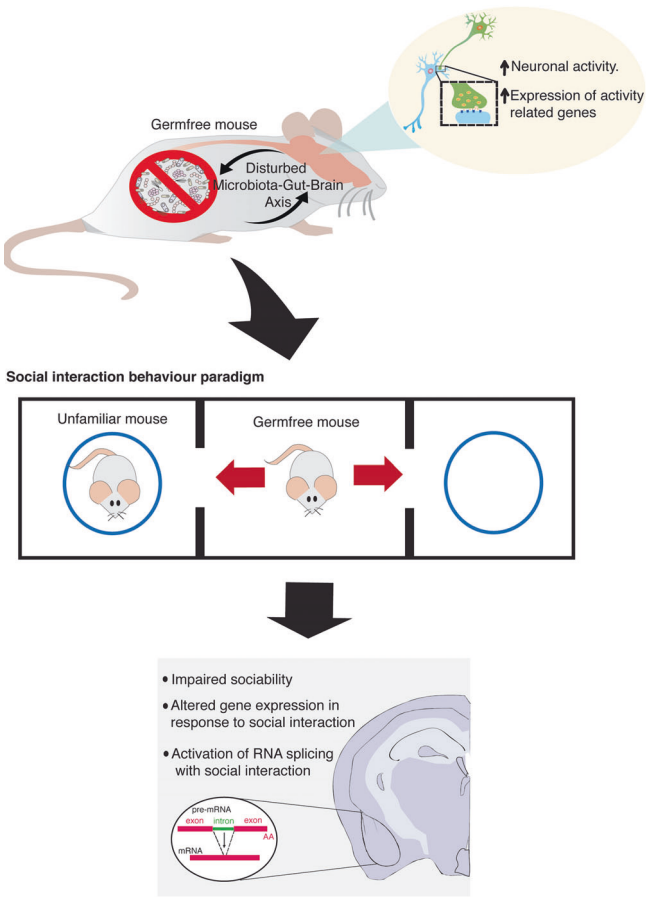
We are living in a microbial world with our bodies having as many microbial cells as human cells. Growing evidence implicates these microbes, known collectively as the microbiome, as key regulators of brain function and behaviour [1]. One of the key findings from across many species is that the microbiome affects social behaviour [2]. We have shown that germ-free (GF) mice, which grow up in a sterile environment and thus have no bacteria in or on their bodies, are less sociable than normal mice[2]. Moreover, the amygdala, a brain region important for social behaviour, is particularly sensitive to changes in microbiome composition [3] and GF mice have widespread changes in amygdala neuronal morphology and function [4].

Ongoing research is trying to determine the molecular mechanisms underpinning such effects. Initially, we exploited unbiased genome-wide transcriptional profiling to determine gene expression in the amygdala of male GF mice. We found differential gene expression, exon usage and RNA-editing in GF mice (Fig. 1). We noticed upregulation of several immediate early response genes such as *Fos*, *Fosb*, *Egr2* or *Nr4a1* in association with increased cAMP response element-binding protein (CREB) signalling in GF mice [5]. In addition, we found differential expression and recoding of several genes implicated in a variety of neuronal processes such as neurotransmission, neuronal plasticity, metabolism and morphology. These data strongly suggest altered baseline neuronal activity in the amygdala of GF animals, which may underpin the social deficits. However, what happens under a social stimulus remained known.

To this end we recently described dynamic regulation of several previously undescribed pathways in response to social stimulation. These include regulation of RNA-processing non-coding RNAs that are crucially involved in splicing regulation. Moreover, social stimulus evoked an increase in transcripts of genes involved in neuronal activity, which includes induction of several well established immediate early genes such as *Fos* or *Arc*, the MAP-K pathway and neurotrophic signalling via *Bdnf*. Moreover, we find upregulation of complement components, which have lately been established to be necessary for synaptic rearrangements and plasticity upon neuronal activity [6].



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