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Capgras syndrome induced by Ketamine in a Healthy Subject

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Keywords

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We would like to report a case of Capgras syndrome in a healthy subject, which was induced by ketamine, [an antagonist of the N-methyl D-aspartate (NMDA) subtype of glutamate receptors]. We believe this is the first report of delusion-like misidentification following controlled administration of a psychotomimetic drug, raising the possibility that the neurochemical and cognitive mechanisms through which ketamine acts may also contribute to endogenous misidentification syndromes.

In Capgras syndrome the affected individual believes that a person familiar to them has been replaced by an impostor [1]. Sufferers report minor alterations in the physical identity of the person, which they have difficulty characterizing and sometimes also believe that their own identity has been transformed.

A 26 yr old healthy graduate student carefully screened for medical, neurological, psychiatric problems participated in a 4 day study during which she was administered active (2 mg) or placebo oral lorazepam followed by active (1-minute bolus of 0.42 mg/kg followed by a constant infusion of 0.0085 mg/kg/min for 1 hour) or placebo ketamine in a double-blind, randomized design. Within ten minutes of the active ketamine bolus infusion, she reported moderate anxiety, decreased energy and perceived both a slowing and hastening of time, but was otherwise alert and oriented. Fifteen minutes after the completion of the maintenance dose when her mental status returned to baseline, she reported: "every time you left the room, I thought another person dressed in your clothes was coming back into the room...it wasn't scary, just another person dressed in your clothes, doing your job but the person was a little older in age and weighed more." She also reported: "I'd look into the mirror and think that's not me, I didn't think the image staring back at me was myself..."

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even the words I was saying were not words I would normally say...it just wasn't me... it wasn't my speech, my voice, my reactions...I felt like a different person because I would not have reacted in the way I usually would have." Brief Psychiatric Rating Scale [2] scores increased (19 at baseline to 52 post-bolus) with increases in paranoia, grandiosity, hallucinatory behavior and anxiety. Total score on the Clinician Administered Dissociative States Scale [3] increased from 0 to 30 with highest scores in the factors of unreality, misperception of time and the environment. Neuropsychological testing revealed no significant disturbance of attention or frontal lobe function although there were memory deficits, a dysfunction in post distraction and delayed recall. All her symptoms resolved by the end of the test day. She did not experience delusional misidentification on the day that she received ketamine and lorazepam.

Discussion

Ketamine precipitated a transient delusion-like misidentification resembling the Capgras syndrome in a healthy subject. Although ketamine antagonizes NMDA receptors, it also increases AMPA receptor stimulation [4]. A recent neurocomputational model of cortical hierarchies implicates both of these receptor systems in the healthy brain's calculation of and response to uncertainty; NMDA receptor based mechanisms confer prior expectancies, whereas errors in prediction are specified via AMPA signaling [5]. Ketamine impairs both of these mechanisms, inducing a sense of surprise and unfamiliarity for even the most mundane events [6]. Likewise, cognitive models of delusional misidentification suggest that it arises when learned expectancies fail to constrain current perceptual inputs specifically through a dysfunctional integration of expectancy with experience [7]. The resultant aberrant prediction error engenders a perceived lack of familiarity for someone who is nevertheless familiar. Moreover, individuals suffering from delusional misidentification following neurological insult very often have damage to the right frontal cortex [8], a region whose activity is associated with prediction error driven learning [9]. Ketamine too engenders aberrant right frontal prediction error responses and delusion-like ideas [10].

Some have questioned whether an acute ketamine infusion can engender delusions [11] since the phenomenology is transient and subjects describe their experiences using relative terms ('it was as if...') although some subjects do report a high degree of certainty retrospectively [12]. Rather than delusions *per se*, ketamine may be a good model for the 'delusional mood' [13] that attends the very early phases of psychosis [14], here patients report: '*Wherever you are looking, everything looks unreal.*' Or '*People went down the street like in a puppet theatre*' [15]. Furthermore: '*People look confusing...they are almost like they're made up...people that I know...have masks on or they are disguising themselves. It's like a play...like a big production story*' [16]. Crucially, the patients in these reports use the same relative terms as our subject – 'like' or 'almost like'. We suggest that the present subject was experiencing a particular type of delusional mood that would lead them to construct a Capgras delusion (had the ketamine infusion continued or been administered at a higher dose).

Ketamine has been administered to healthy volunteers for research purposes on numerous occasions by multiple investigators. Why has Capgras syndrome not been recorded previously? It is possible that other subjects had a similar experience but were either too cognitively impaired or paranoid to describe it [12], alternatively, it may be that they were not asked the right questions. Finally it could be that this is an extremely rare manifestation of ketamine's psychotomimetic effects, a result of the considerable inter subject variability in the phenomenology of the ketamine experience [10, 12, 17].

We urge others who undertake ketamine research to question their subjects regarding misidentification experiences. Prior work has shown that a portion of the variability in ketamine's effects may be accounted for by variation in the neural circuitry engaged in performing cognitive tasks [10, 17]. It may be that ketamine infusion engenders impairments in face processing that have hitherto gone undetected. There are candidate biochemical mechanisms for delusional misidentification [18] and, should we be able to identify other subjects with similar experiences, we could begin to address those models empirically.

The present finding underlines the utility of ketamine as a means to explore the genesis of delusions and suggests that glutamatergic dysfunction may be involved in the pathophysiology of delusional misidentification.

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