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Title:

Ketamine-induced disruption of verbal self monitoring linked to superior temporal activation

Running Title:

Ketamine-induced self monitoring misattributions

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Abstract

Rationale

Auditory hallucinations and delusions are hypothesized to arise from faulty monitoring of self-generated actions. Misattribution of self-generated speech is a commonly observed in schizophrenic patients with these symptoms, and the neural correlates show increased activation in the lateral temporal cortex. Neuroimaging studies in schizophrenia are often confounded by medication effects and illness chronicity. A pharmacological model of schizophrenia is provided by ketamine, a *N*-methyl-D-aspartate (NMDA) antagonist.

Objectives

We sought to test the following hypotheses: 1) ketamine increases the misattribution of distorted self-generated speech, and 2) ketamine-induced external misattributions are associated with increased lateral temporal activation.

Methods

Participants were 8 healthy male volunteers, naïve to ketamine (mean age 28.0 years). Ketamine (0.23mg/kg bolus followed by 0.64mg/kg/h) and placebo infusions were administered in a double-blind, randomized order, in conjunction with 2 functional magnetic resonance imaging (fMRI) sessions. Each fMRI session consisted of a verbal self-monitoring task in which auditory feedback was experimentally modified.

Results

Ketamine was associated with psychotic and dissociative symptoms, reflected in increased ratings in the Brief Psychiatric Ratings Scale and the Clinician Administered Dissociative States Scale. Subjects made more misattributions of distorted self-generated speech ($p < 0.02$) during the ketamine infusion relative to placebo. Ketamine-induced misattributions were associated with left medial and

superior temporal activation, while misattributions during placebo showed a relative reduction in lateral temporal activation.

Conclusions

These data are consistent with the notion that self-monitoring impairments underlie psychotic symptoms and suggest that NMDA receptor dysfunction may mediate self-monitoring deficits and psychotic phenomena in schizophrenia.

Introduction

One of the key psychopathological features of schizophrenia is the tendency to attribute certain perceptual experiences to an external source (Costafreda et al. 2008). For example, affected individuals classically report that their actions or thoughts are being controlled by an external agency, termed a delusion of passivity. It has been proposed that auditory hallucinations have a similar basis in which thoughts or subthreshold vocalisations are incorrectly identified as being spoken by an external person or entity (Feinberg 1978; Frith and Done 1988).

Actions and thoughts arising from willed intention (rather than in response to external stimuli) have been hypothesised to be recognized as originating from oneself through the creation of an internal (efference) copy of the intended action, which is then compared to new sensory inputs (Wolpert et al. 1995). If incoming sensory inputs match the expected self-generated action, then the internal response to the sensory inputs is reduced, the sensation arising from the action being identified as self-generated. In schizophrenia it is postulated that generation of the efference copy is impaired, leading to misattribution of self-generated actions, thoughts, and feelings as arising from an external entity (Feinberg 1978; Frith and Done 1988).

Compared to healthy controls, patients with schizophrenia have a greater tendency to attribute self-generated speech that has been distorted in real-time to an external agency (Johns and McGuire 1999; Johns et al. 2001). In healthy individuals, correct identification of distorted, self-generated speech was associated with increased blood oxygenation level dependent (BOLD) responses in bilateral temporal cortices, while *mis*-identifications were associated with reduced temporal BOLD responses (Fu et al. 2006). However, in schizophrenic patients with auditory hallucinations, *mis*-identifications were associated with an increased temporal BOLD response, in

contrast to the reduced temporal activation found in controls and schizophrenic patients in remission (Fu et al. 2008).

The self-monitoring aspect of the forward model is thought to be dependent on coherent fronto-temporal neuronal burst firing, which is abnormal in schizophrenia (Mechelli et al. 2007). It has been hypothesized that dysfunctional GABAergic interneurons are central to the loss of coherent firing in schizophrenia (Lewis et al. 2005). Dysfunction of GABA interneurons may also occur through the administration of an uncompetitive NMDA receptor antagonist such as ketamine (Moghaddam et al. 1997; Olney and Farber 1995; Olney et al. 1999), which induces effects similar to the symptoms of schizophrenia (Krystal et al. 1994). In healthy individuals, ketamine increases the BOLD response to neutral faces (Abel et al. 2003), modulates prefrontal BOLD responses to verbal fluency in conjunction with task demand (Fu et al. 2006), and impairs hippocampal function during encoding and retrieval (Honey et al. 2005). Fronto-temporal function during verbal monitoring has also been reported to predict individual psychotogenic effects of ketamine – suggesting this network may be a key target for NMDA receptor blockade in psychosis generation (Honey et al. 2008). The effects of ketamine may give rise to the abnormal mismatch detection and salience attribution (Corlett et al. 2007) that is commonly observed in schizophrenia (Johns and McGuire 1999; Johns et al. 2001). Thus, ketamine may be expected to impair generation or monitoring of the efference copy and so lead to a similar increase in misattribution of distorted self-generated speech as observed in schizophrenic patients with auditory hallucinations.

Here we test the following hypotheses: ketamine leads to: a) an increase in misattribution of distorted self-generated speech, and b) this will be associated with lateral temporal activation.

Methods

Subjects

Ten healthy, native English speaking, right-handed male, ketamine naïve volunteers were recruited. All subjects provided written informed consent, and ethical approval was provided by the Institute of Psychiatry and Maudsley NHS Trust. One subject only partially completed both scan sessions due to discomfort from the intravenous line, and technical problems during the scans for another subject precluded full acquisition of his data. Data from the remaining eight male volunteers, mean age 28.0 years (SD 5.9 years), mean IQ 109.0 (SD 7.9) are presented.

Ketamine and Placebo Infusions

Subjects received either intravenous placebo (normal saline solution) bolus over 30 seconds followed by a saline infusion or a ketamine bolus of 0.23 mg/kg over 30 seconds followed by an infusion of 0.65 mg/kg/h administered in a double-blind manner, at two separate scan sessions separated by a minimum of one day. The order of infusions was randomised across patients. Heart rate and blood pressure were measured prior to the intravenous bolus, immediately following the bolus, and at 10 minute intervals throughout the scan. The Brief Psychiatric Rating Scale (BPRS) and the Clinician Administered Dissociative States Scale (CADSS) (Bremner et al. 1998) were administered at the beginning and end of each scan session.

Verbal Self Monitoring Task

Subjects viewed single adjectives and were asked to read aloud the visually presented word. When subjects read aloud the word, their voice was transmitted by a MRI compatible microphone through a software program and relayed back through an acoustic MRI sound system. Subjects reported that they heard the verbal feedback in 'real-time' without any perceptible delay (Johns and McGuire 1999; Johns et al. 2001).

The verbal feedback was one of four conditions: (A) self-undistorted feedback: subject's own voice; (B) self-distorted feedback: subject's own voice lowered in pitch by four semitones; (C) alien-undistorted feedback: a pre-recorded male voice unknown to the participant; (D) alien-distorted feedback: a pitch distorted version of the pre-recorded male voice, lowered by four semitones. There were two source of verbal feedback: self or other (alien); and two levels of distortion: 0 or - 4 semitones. Subjects were asked to determine the source of the feedback. There were three possible responses: (1) self, (2) other, (3) unsure. Subjects pressed a button box to indicate their decision. Reaction time and response were measured for each stimulus.

Words were presented for 750 ms within a rectangular outline on a visual display unit. Beneath the words were the letters 'S' 'U' 'O', each within a square outline, representing the possible responses of 'self', 'unsure' or 'other', respectively.

When subjects read aloud the presented word, their voice was transmitted by a MRI compatible microphone fixed at 5 cm in front of the subject's mouth. Their speech was transformed through a software program and a DSP.FX digital effects processor (Power Technology, California, USA) then amplified by a computer sound card and relayed back to the subject through an acoustic MRI sound system (Ward Ray-Premis, Hampton Court, UK) and pneumatic tubes within the ear protectors at a volume of 91 $\pm$ 2 dB.

The verbal feedback was one of four conditions as described above. In the alien-undistorted and alien-distorted feedback conditions, a voice-key picked up the onset of the subject's verbal response and substituted a pre-recorded version of the same word.

Subjects were instructed to press the 'S' button if they thought that the auditory verbal feedback was their voice or a distorted version of their voice, or to press the 'O' button if they believed that it belonged to someone else or was a distorted version of another person's voice, or to press the 'U' button if they were unsure of the source of the feedback. Responses were made with a button box held in the right hand with three buttons corresponding to the possible responses. Subjects were asked to use their right thumb to press each button. When subjects made their response, the corresponding letter changed colour from dark blue to grey.

Each set of trials began with the word 'begin' followed by 32 individual word trials and 3 'baseline' trials which were presented after every eighth word trial (presented as an empty rectangle during which subjects made no response while the response letters remained). Each set of trial consisting of 36 stimuli as described and shall be referred to as a "run".

Each condition (a total of 4 conditions as described above) was pseudo-randomly presented eight times within each run based on a predetermined playlist. There was a total of six possible runs, and subjects participated in 3 runs during the scan session for a total of 96 words (24 trials for each condition). The order of runs was randomised for each subject and between subjects.

fMRI scan acquisition

T2*-weighted volume images were acquired on a 1.5 Tesla GE Signa System retrofitted with Echo Planar Imaging capability (General Electric, Milwaukee, USA) at the Maudsley Hospital, South London and Maudsley NHS Trust, UK. Twelve non-contiguous axial planes (7 mm thickness, slice skip 1 mm) parallel to the anterior commissure-posterior commissure (AC-PC) line were collected over 1100 ms in a

'clustered' acquisition (TE 40 ms, 70° flip angle). A relative silent period of 2150 ms followed for each stimulus with a TR of 3250 ms. Subjects were able to make their button press response within 4000 ms. Five volumes were collected for each stimulus, for an ISI of 16250 ms. The first scan acquisition volume 'triggered' the software program to present the first word of each run ('begin'), and a total of 180 volumes were collected for each experimental run, with a total of 540 volumes (3 runs) for each subject.

fMRI Data Analysis

The data were realigned to the initial volume (Bullmore et al. 1999a) and smoothed by a 2D Gaussian filter at full-width half-maximum 7.2 mm. Responses to the experimental conditions were detected by time-series analysis using Poisson functions with peak responses at 4 and 8 s. Each condition was convolved separately with the Poisson functions to yield two models of the expected haemodynamic response. The weighted sum of the two convolutions that gave the best fit to the time series at each voxel was computed as the ratio of the sum of squares of deviations from the mean intensity value due to the model divided by the sum of squares due to the residuals, the sum of squares quotient (SSQ) ratio. In order to sample the distribution of the SSQ ratio under the null hypothesis, the time series at each voxel was permuted using a wavelet-based resampling method repeated 10 times at each voxel (Bullmore et al. 2001), and the data combined over all intracerebral voxels resulting in 10 permuted parametric maps of the SSQ ratio at each plane for each subject. Combining these data yielded the distribution of SSQ ratio under the null hypothesis. The observed and randomized SSQ ratio maps were transformed into standard space by a rigid body transformation onto a high-resolution inversion recovery image from the same subject, followed by an affine transformation onto a Talairach and Tournoux (1988) template. A brain activation map was

produced for each condition by testing the median observed SSQ ratio at each intracerebral voxel in standard space (Brammer et al. 1997) against a critical value of the permutation distribution for median SSQ ratio from the spatially transformed wavelet-permuted data. Only activations in-phase with the BOLD response were included in the analysis. In order to increase sensitivity and reduce the number of statistical comparisons, hypothesis testing was carried out at the cluster level (Bullmore et al. 1999b). Rather than set a single a priori p value below which findings are regarded as significant, the number of clusters that would be expected by chance alone for a range of p values was calculated. The statistical threshold for cluster significance for each analysis was then set such that the expected number of false-positive clusters by chance alone would be less than one (Bullmore et al. 1999b).

Analysis of variance was carried out on the SSQ ratio maps by computing the difference in mean SSQ ratio between conditions and using a null distribution obtained by random permutation of condition membership and re-computation of the mean SSQ ratio difference. BOLD response during correct and incorrect responses to self-distorted feedback was examined during the placebo and ketamine infusions.

Results

Behavioral effects of ketamine

Distinct differences were evident in behavioral responses to ketamine. Most subjects developed thought disorder, and a few reported paranoid ideation and visual illusions following the ketamine infusion. Mean total BPRS ratings increased significantly from 0.9 $\pm$ 0.7 with placebo to 9.6 $\pm$ 4.7 with ketamine (F $_{1,13}$ = 26.9, $P < 0.001$) and mean CADSS ratings from 0.1 $\pm$ 0.4 with placebo to 22.4 $\pm$ 17.8 with ketamine (F $_{1,13}$ = 12.7, $P < 0.003$). The changes in the BPRS and CADSS ratings reflected increases in thought disorder, suspiciousness, depersonalisation, elation and psychomotor excitation. Despite the changes in mental state, these were not

reflected in behavior during the scan – subjects remained still, and were fully compliant with the procedure for the duration of the image acquisition. All subjects recovered fully following completion of the experiment.

Performance on verbal self-monitoring task

Comparison of responses between trials was performed by a repeated measures MANOVA with the following within group factors: source of feedback (self or alien), level of distortion (none or with distortion), and presence of ketamine (placebo or with ketamine), for each of the possible responses: correct attributions, misattribution errors and unsure responses.

For correct responses, there were trends towards a main effect of source ($F_{1,7} = 5.1$, $P = 0.06$) with more correct responses during the self feedback conditions and towards a main effect of distortion ($F_{1,7} = 5.0$, $P = 0.06$) with more correct responses during the undistorted feedback conditions. A significant interaction of source by distortion was observed ($F_{1,7} = 28.4$, $P < 0.001$): subjects made fewer correct responses with increasing distortion during the self feedback conditions but distortion did not have a significant effect on performance during alien feedback conditions (Table 1). Neither a main effect of ketamine nor any interactions with ketamine were found.

For misattributions, an interaction of source by distortion was observed ($F_{1,7} = 9.0$, $P < 0.02$): subjects made more external misattributions with distortion during the self-feedback conditions and a minimal change in response with distortion during the alien feedback conditions.

For unsure responses, there was a significant main effect of distortion ($F_{1,7} = 5.9$, $P < 0.05$): subjects made more unsure responses during the distorted feedback trials,

and there was an interaction of source by distortion ($F_{1,7}$ = 5.9, P < 0.05): subjects made more unsure responses made with increasing distortion during the self feedback conditions but not during the alien feedback conditions.

As the hypothesis was that a ketamine-induced psychotic state would be associated with an increased number of external misattributions during the self-distorted feedback condition, this was explicitly examined. A significant main effect of ketamine was found ($F_{1,7}$ = 8.2, P < 0.02): subjects made more external misattribution errors during the ketamine infusion than placebo.

Reaction times for each feedback condition

Comparison of mean reaction times between trials was performed by a repeated measures MANOVA with the following within group factors: source of feedback (self or alien), level of distortion (none or with distortion), and presence of ketamine (placebo or with ketamine), for each of the possible responses: correct attributions, misattribution errors and unsure responses.

For correct responses, there was a significant main effect of source ($F_{1,6}$ = 9.9, P < 0.02): subjects were faster to respond during the alien feedback conditions, and a significant main effect of distortion ($F_{1,6}$ = 35.2, P < 0.001): subjects had slower reaction times during the distorted feedback conditions. A significant interaction of source by distortion was observed ($F_{1,6}$ = 15.9, P < 0.007): subjects were proportionally slower with increasing distortion during the self feedback conditions but distortion had little effect on reaction time during the alien feedback conditions. Neither a main effect of ketamine nor any interactions with ketamine were found.

For misattribution errors, as only 2 subjects made external misattribution errors during the self-undistorted feedback condition with placebo, this condition was

excluded from the analysis. During the self-distorted feedback condition, no significant main effect of drug was observed (paired t-test, t = 0.42, df = 4, p = 0.70). For the alien conditions, there were no main effects of distortion nor of drug, and nor interaction of distortion by drug.

For unsure responses, as only 2 subjects made external misattribution errors during the self-undistorted feedback condition with ketamine, this condition was excluded from the analysis. During the self-distorted feedback condition, no significant main effect of drug was observed (paired t-test, t = 0.35, df = 3, p = 0.75). For the alien conditions, there were no main effects of distortion nor of drug, however a distortion by drug interaction was found (F $_{1,3}$ = 40.1, P < 0.008): subjects had faster reaction times with increasing distortion during the placebo condition, but the inverse pattern during the ketamine condition.

Effect of ketamine during self-distorted feedback on BOLD response

Ketamine, compared to placebo, led to reduced BOLD response in the left superior temporal gyrus during self-distorted speech (BA 22 extending to BA 42) regardless of whether the feedback was correctly identified as self ({- 61, - 41, 4} to {-58, -33, 20} cluster size 43 voxels) or misidentified as alien ({- 51, - 22, - 2} to {-61, -33, 9} cluster size 68 voxels). During trials where feedback was misidentified, there was additional reduced activation in right retrosplenial cortex (BA 17 {7, -81, 4} to {7, -74, 9} cluster size 39 voxels), whereas during correctly identified trials, there was reduced activation in posterior cingulate cortex (BA 29 {4, - 30, 20} cluster size 10 voxels).

BOLD response during self-distorted feedback - placebo

During placebo infusion, correctly (vs. incorrectly) identified self-distorted feedback was associated with increased superior temporal BOLD response bilaterally (BA 22 extending to BA 42 - right extending from {58, - 26, - 7} to {51, - 41, 15} cluster size

62 voxels; left extending from {- 61, - 26, 9} to {- 58, - 26, 20} cluster size 116 voxels), and midline cerebellum ({- 7, - 96, - 24} cluster size 9 voxels). No regions showed any activation during misattribution of self-distorted feedback on placebo.

BOLD response during self-distorted feedback - ketamine

Correct (vs. incorrect) attribution of self-distorted feedback during ketamine infusion led to similarly increased BOLD response in temporal cortex bilaterally (right middle temporal cortex - BA 21 {54, - 48, - 7} to {54, - 41, - 2} cluster size 20 voxels, left superior temporal cortex - BA 42 {- 58, - 19, 20} cluster size 14 voxels) and in left ventrolateral prefrontal cortex (BA 47 {-36, 30, - 2} cluster size 7 voxels). However, misattribution during ketamine infusion also led to a relative increase in BOLD in right superior temporal cortex (BA 22 {- 36, - 41, 20} cluster size 15 voxels, extending to Heschl's gyrus, BA 41 {- 40, - 30, 9} cluster size 10 voxels; see fig 1).

Discussion

This is the first study to examine the relationship between misattribution of distorted self-generated speech and BOLD response during ketamine infusion. The small sample size means that the results should be viewed as preliminary. It is conceivable that ketamine effects on motor function might have had an impact on the fMRI results, but there were no visible differences in subject movement between the ketamine and control scans. It is also possible that ketamine effects on blood pressure may have affected the results.

In the presence of ketamine, subjects rapidly developed thought disorder, paranoid ideation and dissociative symptoms, which persisted for the duration of the scan. As expected, subjects made more external misattributions in the self-distorted feedback condition during the ketamine infusion than with placebo. This was the only condition in which task performance was significantly affected by ketamine. The increased

frequency of misattributions was similar to that observed in acutely psychotic patients with schizophrenia, who make more misattribution errors in this feedback condition than schizophrenic patients in remission and healthy controls (Johns and McGuire 1999; Johns et al. 2001).

The impairment in behavioral performance was not simply due to the propensity to attribute all ambiguous stimuli to an external source, suggested to be an alternative explanation to the efference-copy hypothesis (Allen et al. 2004), as 'other' attributions during the alien-distorted feedback condition were no more common following ketamine than placebo (Table 1). The finding of increased misattribution of self-distorted speech contrasts with a previous report that ketamine in healthy controls did not induce a schizophrenia-like external misattribution of remembered self-generated words (Honey et al. 2006; Keefe et al. 1999).

During the placebo infusion, correct recognition of the source of the feedback relative to misattributions was associated with greater bilateral temporal activation, consistent with findings in another group of healthy volunteers (Fu et al. 2006). During the ketamine infusion, external misattributions of self-distorted speech were associated with greater activation in the left superior temporal gyrus relative to correct responses. The effect of ketamine was similar to that observed in patients with schizophrenia with active hallucinations and delusions, who showed increased lateral temporal activation with external misattributions (Fu et al. 2008). Thus, not only did ketamine increase the frequency of misattribution errors during self-distorted feedback, but it also modified activation in the temporal cortex in association with these errors. Both the behavioural performance and neural correlates resembled the pattern of response found in acutely psychotic patients with schizophrenia (Cahill 1996; Fu et al. 2008; Johns and McGuire 1999; Johns et al. 2001).

These findings should be interpreted in light of the fact that ketamine led to lower activation than placebo during all self-distorted trials, whether correctly or incorrectly identified, suggesting a lower neural activation in response to unexpected sensory inputs, possibly representing reduced comparison with the efference copy. It might thus be hypothesized that there are 3 possible levels of temporal cortex activation – the highest level corresponding to correctly identified, distorted self-generated speech, which in the presence of a working efference copy mechanism would lead to the highest level of mismatch between the expected and perceived signal. The intermediate level of activation might represent either misidentified self-generated distorted speech, or alien undistorted speech, having an intermediate level of mismatch with the expected signal (Fu et al. 2006). The lowest level of activation might occur only with correctly identified undistorted self-generated speech or distorted self-generated speech without a working efference copy mechanism (which, because of the absence of expectation, would appear to the individual as normal self-generated speech).

The findings thus offer support for the theory of impaired verbal self-monitoring underlying hallucinations and delusions in schizophrenia (Feinberg 1978; Frith and Done 1988) and suggest that self-monitoring deficits and psychotic symptoms in schizophrenia may result from changes in glutamate activity at NDMA receptors. However, it should be noted that subjects did not experience severe psychotic symptoms with ketamine but rather a mild symptomatology, which is consistent with the dosage used (Krystal et al. 1994). It has been previously reported that the effects of ketamine do not map directly onto those symptoms seen in schizophrenia, with illusions and delusion-like ideas being most prominent (Pomarol-Clotet et al. 2006). Nonetheless, in the present study, subjects still showed impaired self-monitoring performance, suggesting that such impairments may be evident at early stages of a psychotic illness prior to the development of full psychotic features. This could be

investigated by applying the self-monitoring paradigm in individuals with prodromal symptoms of psychosis.

In summary, ketamine infusion was associated with impaired self-monitoring performance consistent with that observed in schizophrenic patients with auditory hallucinations and delusions. Moreover, the effect on lateral temporal activation was comparable to the neural correlates of misattribution errors in schizophrenia. The specificity of the brain activation during the self-monitoring task indicates that the effect was not attributable to other cognitive impairments, nor to a general vascular response. This study offers further support for the cognitive model of verbal self monitoring impairments underlying psychotic symptoms and suggests that self monitoring deficits in schizophrenia and psychotic phenomena may reflect NMDA mediated abnormalities in the temporal cortex.

Disclosure/Conflicts of interest

All authors report no conflicts of interest.

Table 1

Mean(SD) percent correct responses for each condition and auditory stimulus

	Self-undistorted	Self-distorted	Alien-undistorted	Alien-distorted
Placebo condition				
Correct responses	94.4 (9.8)	68.6 (26.2)	49.3 (26.7)	55.9 (19.5)
Misattributions	1.0 (1.9)	15.1 (29.8)	35.8 (26.0)	25.8 (19.5)
Unsure responses	3.6 (7.2)	19.9 (22.2)	15.0 (13.2)	14.6(16.1)
Ketamine condition				
Correct responses	97.5 (3.7)	56.8 (31.6)	52.8 (27.6)	54.9 (19.5)
Misattributions	5.3 (1.5)	25.8 (32.0)	32.4 (20.1)	23.5 (14.0)
Unsure responses	1.5 (3.0)	19.9 (23.4)	9.8 (10.9)	16.3 (13.4)

Figure Legends

Figure 1

During the ketamine infusion, external misattributions compared to correct attributions of self-distorted speech were associated with relative activation extending from left Heschl's gyrus (BA 41) to the superior temporal gyrus (BA 22). No areas were more activated in association with misattributions during the placebo infusion.

Figure 1.
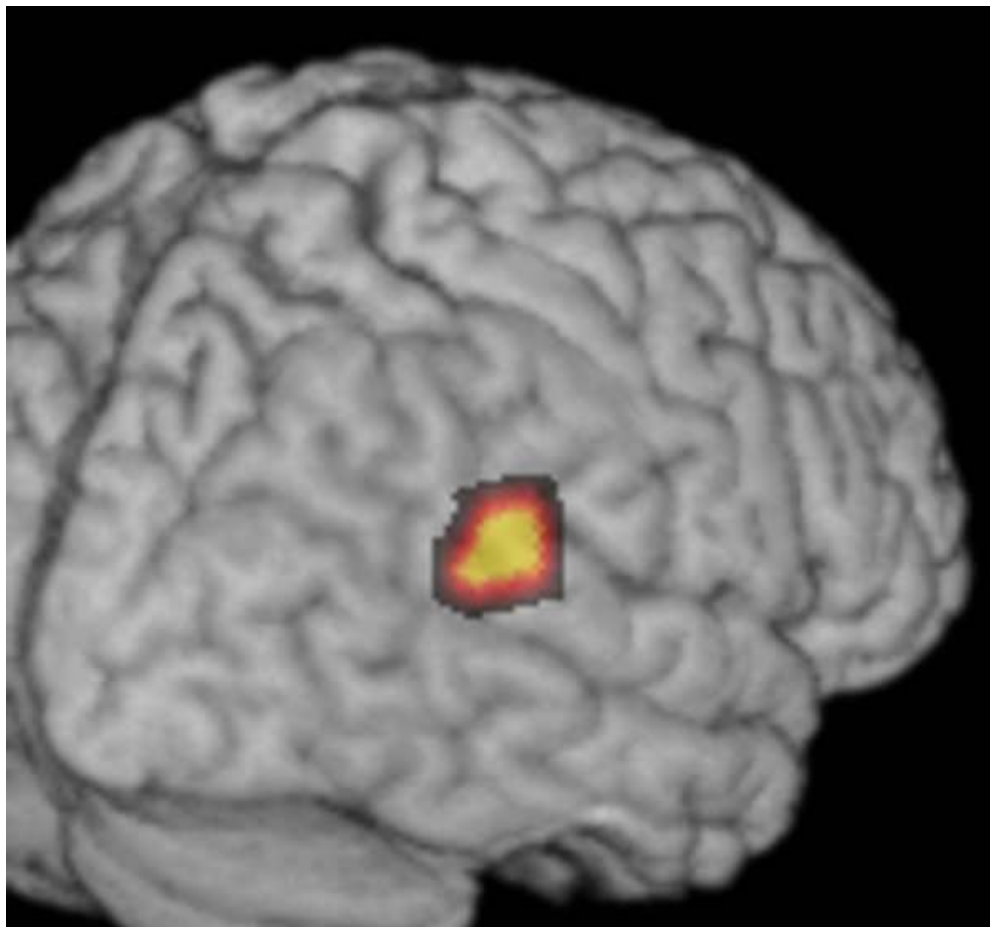
References

Abel KM, Allin MP, Kucharska-Pietura K, David A, Andrew C, Williams S, Brammer MJ, Phillips ML (2003) Ketamine alters neural processing of facial emotion recognition in healthy men: an fMRI study. Neuroreport 14: 387-91

Allen PP, Johns LC, Fu CH, Broome MR, Vythelingum GN, McGuire PK (2004) Misattribution of external speech in patients with hallucinations and delusions. Schizophr Res 69: 277-87

Brammer MJ, Bullmore ET, Simmons A, Williams SC, Grasby PM, Howard RJ, Woodruff PW, Rabe-Hesketh S (1997) Generic brain activation mapping in functional magnetic resonance imaging: a nonparametric approach. Magn Reson Imaging 15: 763-70

Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM (1998) Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress 11: 125-36

Bullmore E, Long C, Suckling J, Fadili J, Calvert G, Zelaya F, Carpenter TA, Brammer M (2001) Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. Hum Brain Mapp 12: 61-78

Bullmore ET, Brammer MJ, Rabe-Hesketh S, Curtis VA, Morris RG, Williams SC, Sharma T, McGuire PK (1999a) Methods for diagnosis and treatment of stimulus-correlated motion in generic brain activation studies using fMRI. Hum Brain Mapp 7: 38-48

Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ (1999b) Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. IEEE Trans Med Imaging 18: 32-42

Cahill C (1996) Psychotic experiences induced in deluded patients using distorted auditory feedback. Cognit Neuropsychiatry 1: 201-11

Corlett PR, Honey GD, Fletcher PC (2007) From prediction error to psychosis: ketamine as a pharmacological model of delusions. J Psychopharmacol 21: 238-52

Costafreda SG, Brebion G, Allen P, McGuire PK, Fu CH (2008) Affective modulation of external misattribution bias in source monitoring in schizophrenia. Psychol Med 38: 821-4

Feinberg I (1978) Efference copy and corollary discharge: implications for thinking and its disorders. Schizophr Bull 4: 636-40

Frith CD, Done DJ (1988) Towards a neuropsychology of schizophrenia. Br J Psychiatry 153: 437-43

Fu CH, Brammer MJ, Yaguez L, Allen P, Matsumoto K, Johns L, Weinstein S, Borgwardt S, Broome M, van Haren N, McGuire PK (2008) Increased superior temporal activation associated with external misattributions of self-generated speech in schizophrenia. Schizophr Res 100: 361-3

Fu CH, Vythelingum GN, Brammer MJ, Williams SC, Amaro E, Jr., Andrew CM, Yaguez L, van Haren NE, Matsumoto K, McGuire PK (2006) An fMRI study of verbal self-monitoring: neural correlates of auditory verbal feedback. Cereb Cortex 16: 969-77

Honey GD, Corlett PR, Absalom AR, Lee M, Pomarol-Clotet E, Murray GK, McKenna PJ, Bullmore ET, Menon DK, Fletcher PC (2008) Individual

differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J Neurosci 28: 6295-303

Honey GD, Honey RA, O'Loughlin C, Sharar SR, Kumaran D, Suckling J, Menon DK, Sleator C, Bullmore ET, Fletcher PC (2005) Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: an fMRI study. Cereb Cortex 15: 749-59

Honey GD, O'Loughlin C, Turner DC, Pomarol-Clotet E, Corlett PR, Fletcher PC (2006) The effects of a subpsychotic dose of ketamine on recognition and source memory for agency: implications for pharmacological modelling of core symptoms of schizophrenia. Neuropsychopharmacology 31: 413-23

Johns LC, McGuire PK (1999) Verbal self-monitoring and auditory hallucinations in schizophrenia. Lancet 353: 469-70

Johns LC, Rossell S, Frith C, Ahmad F, Hemsley D, Kuipers E, McGuire PK (2001) Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. Psychol Med 31: 705-15

Keefe RS, Arnold MC, Bayen UJ, Harvey PD (1999) Source monitoring deficits in patients with schizophrenia; a multinomial modelling analysis. Psychol Med 29: 903-14

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB, Jr., Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51: 199-214

Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6: 312-24

Mechelli A, Allen P, Amaro E, Jr., Fu CH, Williams SC, Brammer MJ, Johns LC, McGuire PK (2007) Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. Hum Brain Mapp 28: 1213-22

Moghaddam B, Adams B, Verma A, Daly D (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 17: 2921-7

Olney JW, Farber NB (1995) Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52: 998-1007

Olney JW, Newcomer JW, Farber NB (1999) NMDA receptor hypofunction model of schizophrenia. J Psychiatr Res 33: 523-33

Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore ET, Fletcher PC (2006) Psychological effects of ketamine in healthy volunteers. Phenomenological study. Br J Psychiatry 189: 173-9

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, Thieme

Wolpert DM, Ghahramani Z, Jordan MI (1995) An internal model for sensorimotor integration. Science 269: 1880-2