Supplementary Online Content

Beck K, Hindley G, Borgan F, et al. Association of ketamine with psychiatric symptoms and implications for its therapeutic use and for understanding schizophrenia: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(5):e204693. doi:10.1001/jamanetworkopen.2020.4693

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Studies and Data Not Included in Meta-analysis

Effect of ketamine administration to healthy controls: meta-analysis
28 studies[1,2,11–17,3–10 18] met inclusion but were excluded as they were identified as using data that overlapped with studies that were already included in the meta-analysis. 1 study[19] met inclusion criteria but was excluded from the positive symptom meta-analysis as they were identified as using data that overlapped with other studies already included.

18 studies [15,20,29–36,21–28] did not respond to two requests for data prior to submission.
[37–45] replied to the request for data but were unable to provide raw data from their studies, as it was not available.

3 studies [46–48] replied to the first request for data but were not able to provide data by the time of submission.

Exclusion based on symptom items (meta-analysis of positive and negative symptoms):

Studies that appeared to have data for the positive and negative subscales but had not specified the symptom items included – such that we were not able to determine if the study met inclusion criteria for this part of the meta-analysis were emailed to request the items they included. If studies had data for the total symptoms these studies were also emailed to determine if they had raw data for the positive and symptom subscales

8 studies [49–55] were included in the meta-analysis but were not specifically included in the positive symptom analysis as they did not clearly include the items included in the inclusion criteria.

3 Studies [51–53,55] were included in the meta-analysis but were not specifically included in the negative symptom analysis as they did not clearly include the items included in the inclusion criteria.

1 study [56] was not included in the meta-analysis, this study only included information on positive symptoms and there was no information on the items included.

1 study [57] had a score of 0 for both the S.Ds for the ketamine and control condition for positive symptoms, therefore, this was excluded as the effect size could not be calculated in this situation.

The effects of ketamine in people with schizophrenia
1 study [58] met inclusion criteria but was excluded after author confirmed by email that there was sample overlap with other included studies.

1 study [59] had positive and negative symptom data removed from analysis because author confirmed by email that there was sample overlap with other included studies. Where there was overlap the study with the largest sample size was included.

6 studies [18,31,60–63] all from one group met inclusion criteria but were excluded due to the possibility that there was a sample overlap with a study already included. Information was requested from the author by email.

eMethods 2. Newcastle-Ottawa Assessment Scale for Cohort Studies

		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Kraguljac	2017	unclear	*	*	*	**		*	*
Kort	2017	unclear	*	*	*	*	*	*	*
Duncan	2001	All male	*	*	*	*	*	*	*
Parwani	2005	unclear	*	*	*	*	*	*	*
Rowland	2005	All male	*	*	*	*	*	*	*
Abel	2003	All male	*	*		**	*	*	*
Anand	2000	*	*	*	*	*	*	*	*
Krystal	1998	*	*	*	*	*	*	*	*
Breier	1997	*	*	*		*	*	*	*
Van Berckel	1998	All male	*	*	*	*	*	*	*
Malhotra	1997	*	*	*	*	*	*	*	*
Krystal	1999	*	*	*	*	*	*	*	*
Krystal	2003	*	*	*	*	*	*	*	*
Micallef	2002	22-33 years	*	*	*	*	*	*	*
Rowland	2010	unclear	*	*	*	*	*	*	*
Newcomer	1999	All male	*	*	*	**	*	*	
Stone	2011	All male	*	*		**	*	*	*
Boeijinga	2007	All male	*	*	*	*	*	*	*
Passie	2003	All male	*	*		*	*	*	*
Abdallah	2018	unclear	*	*		*		*	*
Morgan	2011	unclear	*	*		*	*	*	*
Horacek	2010	*	*	*	*	*	*	*	*
Thiebes	2017	All male	*	*	*	*		*	
Powers	2015	unclear	*	*		*		*	*
Mathalon	2014	*	*	*	*	*	*	*	unclear
Hoflich	2015	unclear	*	*	*	*	*	*	*
Nagels	2011	All male	*	*	*	*	*	*	*
Driesen	2013	*	*	*	*	*		*	*
Vernaleken	2013	All male	*	*	*	*		*	*
Krystal	2005	unclear	*	*	*	*	*	*	*
Krystal	2006	unclear	*	*	*	*	*	*	*
Kleinloog	2015	*	*	*		*	*	*	*
D'Souza	2012	unclear	*	*		*	*	*	*
Grent-'t-Jong	2018	*	*	*	*	*		*	*
D'Souza	2018	*	*	*	*	*	*	*	*
Dickerson	2010	unclear	*	*		*		*	unclear

1) **Representativeness of the exposed cohort:** * = “truly representative of average healthy individual in the community” or “somewhat representative of the average healthy individual in the community”
2) **Selection of the non-exposed cohort**:* = “Drawn from the same community as the exposed cohort” (within person design)
3) **Ascertainment of exposure:** * = “Secure record” or “Structured interview” (exposure provided as part of an experiment)
4) **Demonstration that outcome of interest was not present at start of study:** * = “yes” i.e SCID used to screen out people with significant psychopathology
5) **Comparability of cohorts on the basis of the design or analysis:**
    a. * = study controls for prior ketamine use
    b. * = study controls for additional factor/factors
6) **Assessment of outcome:** * = “independent blind assessment” or “record linkage”
7) **Was a follow-up long enough for outcomes to occur**: * = “yes” ie there was sufficient timepoints to show peak psychopathology
8) **Adequacy of follow-up cohorts:** * = “Complete follow-up – all subjects accounted for” or subjects lost to follow-up unlikely to introduce bias – number lost <20% or description provide of those lost”

eMethods 3. Cochrane Tool for Assessment of Bias Within Individual Studies

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Kraguljac 2017	High risk- unblinded	High risk- unblinded	High risk - unblinded	High risk- unblinded	Low risk- no missing data	Low risk – outcomes clear
Kort 2017	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk – outcomes clear
Duncan 2001	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Parwani 2005	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Rowland 2005	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Abel 2003	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Anand 2000	Unclear	Unclear	Low risk	Low risk	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Krystal 1998	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Breier 1997	Unclear	Unclear	Low risk	Low risk	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Van Berckel 1998	Unclear	Unclear	Low risk	Low risk	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Malhotra 1997	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Krystal 1999	Unclear	Unclear	Low risk	Low risk	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for	Low risk- outcomes clear

					missing data across groups	
Krystal 2003	Unclear	Unclear	Low risk	Low risk	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Micallef 2002	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Rowland 2010	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Newcomer 1999	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Stone 2011	Unclear	Unclear	Low risk	Low risk	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Boeijinga 2007	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Passie 2003	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Abdallah 2018	High risk- single blind	High risk-single blind	High risk -single blind	High risk -single blind	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Morgan 2011	High risk – not randomized	High risk – not randomized	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Horacek 2010	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Thiebes 2017	High risk- single blind	High risk-single blind	High risk-single blind	High risk-single blind	Low risk – no missing data	Low risk- outcomes clear
Powers 2015	High risk- unblinded	High risk- unblinded	High risk- unblinded	High risk- unblinded	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Mathalon 2014	Unclear	Unclear	Low risk	Low risk	Low risk – unclear how many drop outs occurred but outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear

Hoflich 2015	Unclear	Unclear	Low risk	Low risk	Low risk – unclear how many drop outs occurred but outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Nagels 2011	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
Driesen 2013	High risk-unblinded	High risk-unblinded	High risk-unblinded	High risk-unblinded	Low risk – no missing data	Low risk- outcomes clear
Vernaleken 2013	High risk-single blind	High risk-single blind	High risk-single blind	High risk-single blind	Low risk – no missing data	Low risk- outcomes clear
Krystal 2005	Unclear	Unclear	Low risk	Low risk	Low risk – unclear how many drop outs occurred but outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Krystal 2006	Unclear	Unclear	Low risk	Low risk	Low risk –<20% drop outs, missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Kleinloog 2015	Unclear	Unclear	Low risk	Low risk	Low risk – no missing data	Low risk- outcomes clear
D'Souza 2012	Unclear	Unclear	Low risk	Low risk	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Grent-'t-Jong 2018	High risk-single blind	High risk-single blind	High risk-single blind	High risk-single blind	Low risk – no missing data	Low risk- outcomes clear
D'Souza 2018	Unclear - blinding status not recorded	Unclear - blinding status not recorded	Unclear - blinding status not recorded	Unclear -blinding status not recorded	Low risk - <20% drop outs and missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups	Low risk- outcomes clear
Dickerson 2010	High risk-single blind	High risk-single blind	High risk-single blind	High risk-single blind	Unclear	Low risk- outcomes clear

Cochrane risk of bias scoring template [64]

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT **Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.**	
Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization);

	• Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following:

	• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;

	• Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.
SELECTIVE REPORTING **Reporting bias due to selective outcome reporting.**	
Criteria for a judgement of 'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS **Bias due to problems not covered elsewhere in the table.**	
Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or

	• Had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.

eMethods 4. Cochrane Tool for Assessment of Bias Across Studies

	Type of bias	Risk of bias across all studies
Random sequence generation	Selection bias	**Unclear risk of bias.** Mostly this is unclear across the studies. However, those that have the required information documented to make a decision are high risk. Therefore there is plausible bias that raises some doubt about the results.
Allocation concealment	Selection bias	**Unclear risk of bias.** Mostly this is unclear across the studies. However, those that have the required information documented to make a decision are high risk. Therefore there is plausible bias that raises some doubt about the results.
Blinding of participants and personnel	Performance bias	Low risk of bias. Plausible bias unlikely to seriously alter the results.
Blinding of outcome assessment	Detection bias	Low risk of bias. Plausible bias unlikely to seriously alter the results.
Incomplete outcome data	Attrition bias	Low risk of bias. Plausible bias unlikely to seriously alter the results.
Selective reporting	Reporting bias	Low risk of bias. Plausible bias unlikely to seriously alter the results.

eMethods 5. Refitting the Model Using r_i's Taking Values 0.1

Acute administration of ketamine generated an increase in psychopathology in healthy participants, seen as a statistically significant increase in the total symptoms (SMD = 1.37, 95% CI, 1.12 to 1.63, P<0.001), positive symptoms (SMD = 1.42, 95% CI, 1.19 to 1.66, P<0.001) and negative symptoms (SMD =1.04, 95% CI, 0.85 to 1.23, P<0.001) compared with a placebo condition.

eMethods 6. Refitting the Model Using r_i's Taking Values 0.7

Acute administration of ketamine generated an increase in psychopathology in healthy participants, seen as a statistically significant increase in the total symptoms (SMD = 1.59, 95% CI, 1.30 to 1.88 , P= <0.001), positive symptoms (SMD = 1.64, 95% CI, 1.35 to 1.93, P< 0.001) and negative symptoms (Standardised mean change score =1.24, 95% CI, 1.04 to 1.44, P<0.001) compared with a placebo condition.

eMethods 7. Comparison of the Effect of Ketamine on Positive and Negative Symptoms Using Correlation Coefficient of 0.1

A comparison of effect sizes demonstrated that ketamine has a greater effect on positive symptoms when compared with negative symptoms (Estimate 0.37, 95% CI=0.13 to 0.61, p=0.003).

eMethods 8. Comparison of the Effect of Ketamine on Positive and Negative Symptoms Using Correlation Coefficient of 0.7

A comparison of effect sizes demonstrated that ketamine has a greater effect on positive symptoms when compared with negative symptoms (Estimate 0.36, 95% CI=0.11 to 0.61, p=0.004).

eMethods 9. Heterogeneity Statistics for Subgroup Analyses

Total psychopathology

Ketamine preparation
I^2 value for racemic ketamine preparation is 73.86%
I^2 value for s-ketamine preparation is 80.34%

Blinding method
I^2 value for double blind studies is 70.60%
I^2 value for unblinded/single blind studies is 83.50%

Infusion method
I^2 value for the studies including the bolus followed by continuous infusion method is 79.43%
I^2 value for the studies including the continuous infusion alone method is 50.73%

Single-day versus multiple-day studies
I^2 value for single-day studies is 0%
I^2 value for multiple-day studies is 63.38%.

Positive psychotic symptoms

Ketamine preparation
I^2 value for racemic ketamine preparation is 78.28%
I^2 value for s-ketamine preparation is 63.81%

Blinding method
I^2 value for double blind studies is 79.48%
I^2 value for unblinded/single blind studies is 60.96%

Infusion method
I^2 value for the studies including the bolus followed by continuous infusion method is 72.38%.
I^2 value for the studies including the continuous infusion alone method is 27.71%

Single-day versus multiple-day studies
I^2 value for single-day studies is 0%
I^2 value for multiple-day studies is 83.00%

Negative psychotic symptoms

Ketamine preparation
I^2 value for racemic ketamine preparation is 67.24%
I^2 value for s-ketamine preparation is 59.06%

Blinding method
I^2 value for double blind studies is 39.18%
I^2 value for unblinded/single blind studies is 72.04%

Infusion method
I^2 value for the studies including the bolus followed by continuous infusion method is 70.32%
I^2 value for the studies including the continuous infusion alone method is 0%

Single-day versus multiple-day studies
I^2 value for single-day studies is 64.59%
I^2 value for multiple-day studies is 62.56%

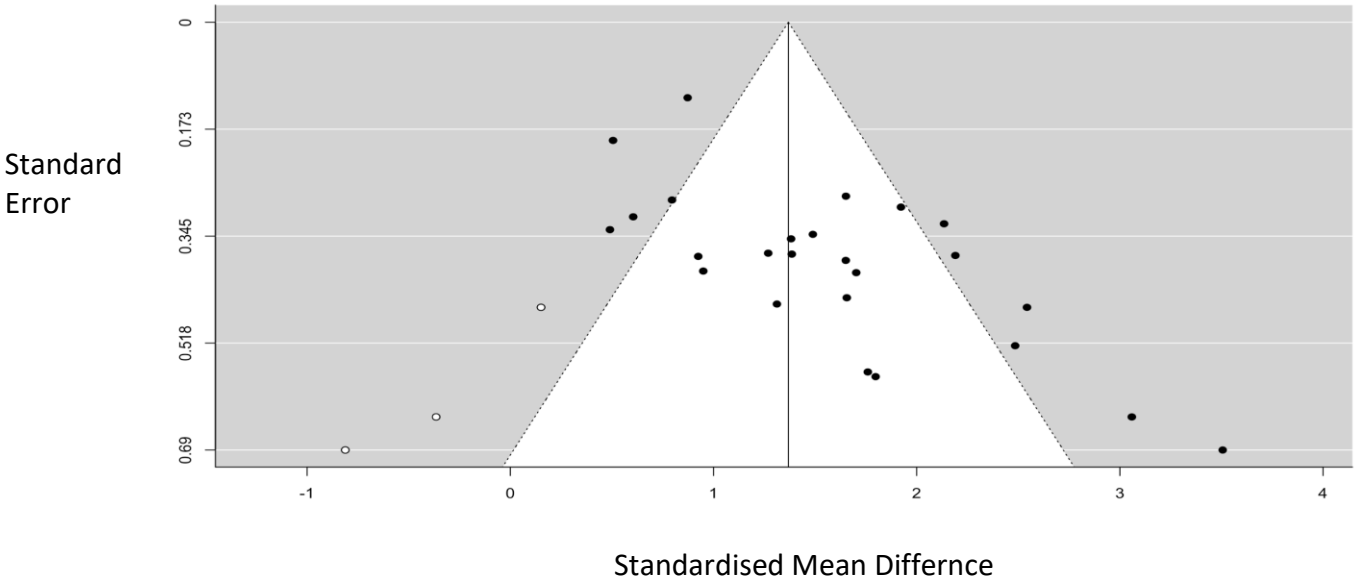
eMethods 10. Subanalyses of Type of Symptom Scale Used

Total psychopathology
The use of both BPRS and PANSS resulted in a statistically significant effect of ketamine on the positive symptoms. (SMD= 1.45, 95% CI, 1.15 to 1.74, p< 0.001, and 1.64, 95% CI, 1.05 to 2.24, p< 0.001 respectively). However, there was no significant difference in the magnitude of the association between the two methods (p=0.56).

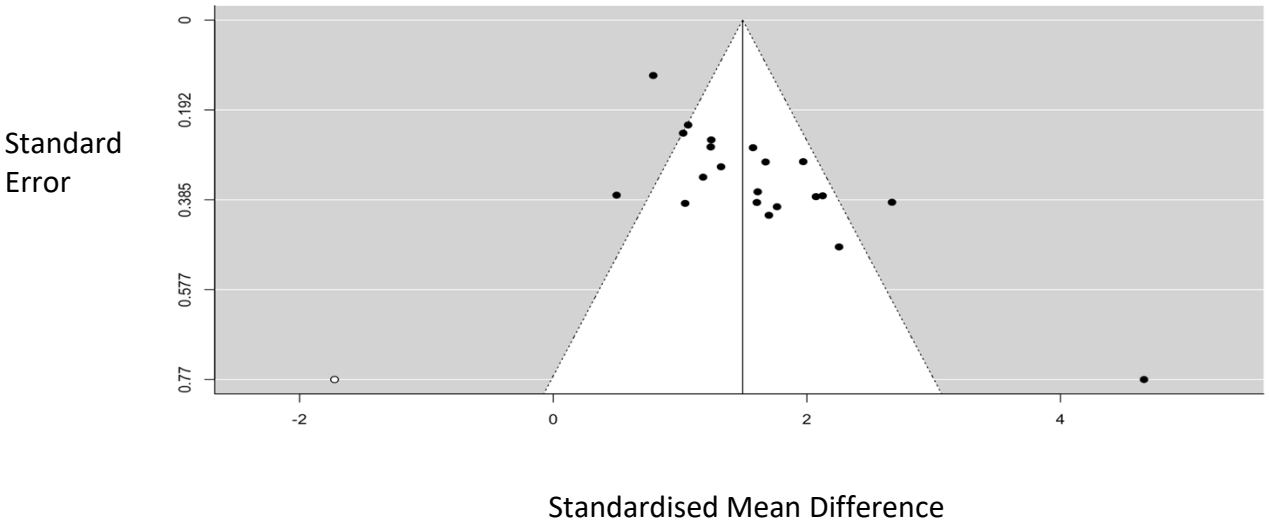
Positive psychotic symptoms
The use of both BPRS and PANSS resulted in a statistically significant effect of ketamine on the positive symptoms. (SMD= 1.68, 95% CI, 0.99 to 2.37, p< 0.001, and 1.52, 95% CI, 1.23 to 1.81, p< 0.001 respectively). However, there was no significant difference in the magnitude of the association between the two methods (p=0.67).

Negative psychotic symptoms
The use of both BPRS and PANSS resulted in a statistically significant effect of ketamine on the positive symptoms. (SMD= 1.27, 95% CI, 0.94, to 1.61, p< 0.001, and 1.09, 95% CI, 0.85 to 1.33, p< 0.001 respectively). However, there was no significant difference in the magnitude of the association between the two methods (p=0.38).

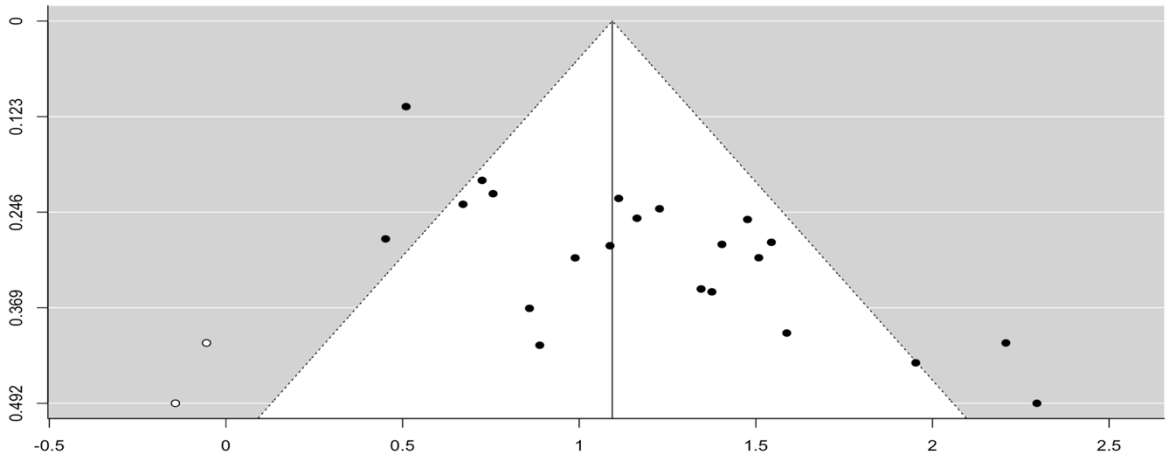
eFigure 1. Funnel Plot for Total Symptoms



eFigure 2. Funnel Plot for Positive Symptoms

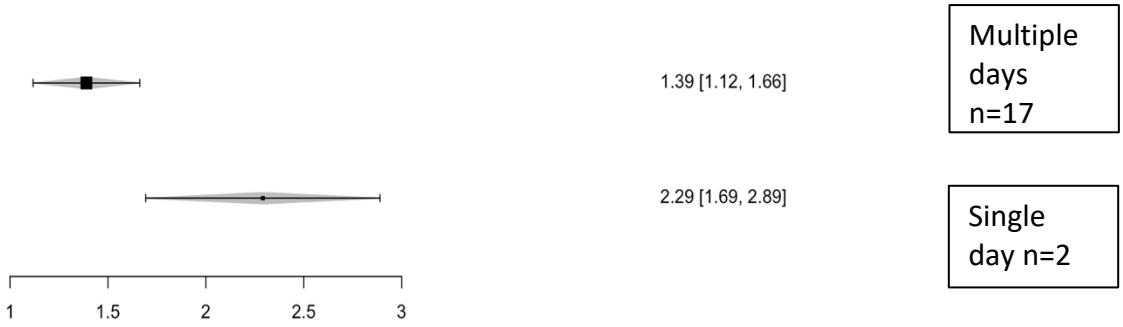


eFigure 3. Funnel Plot for Negative Symptoms

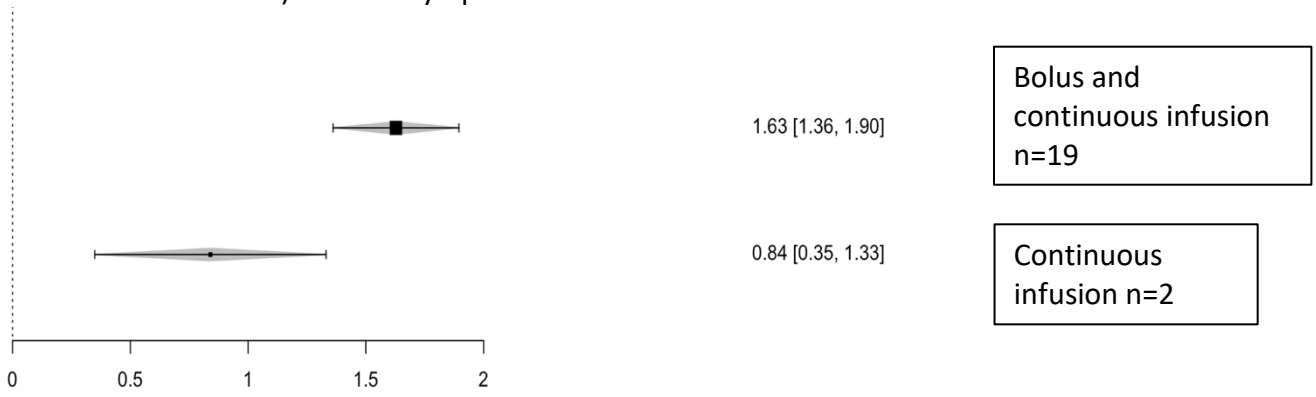


Standardised Mean Difference

eFigure 4. Subgroup Analysis of Single-Day vs Multiple-Day Studies for Total Symptoms



eFigure 5. Subgroup Analysis of Method of Infusion (Bolus and a Continuous Infusion vs Only a Continuous Infusion) Positive Symptoms



eTable 1. Raw Data Used in Total BPRS and PANSS Analysis for Healthy Participants

Author	Year	Sample size	Ketamine mean	Ketamine S.D	Placebo mean	Placebo S.D
Kraguljac	2017	15	32.73	4.94	20.6	0.74
Kort	2017	31	20.52	5.81	8.06	0.25
Parwani	2005	13	27.8	7.3	18.7	1.4
Rowland	2005	10	25.4	8.2	21	8.2
Abel	2003	8	12.1	5.9	1.1	1.1
Van Berckel	1998	18	20.6	1.7	18.2	0.4
Malhotra	1997	16	27.1	6.4	18.7	1.6
Duncan	2001	16	26.4	5.1	18	0.6
Rowland	2010	9	23.8	3.7	20.1	0.4
Newcomer	1999	15	23.36	2.68	19.17	1.5
Stone	2011	8	9.6	4.7	0.9	0.7
Passie	2003	12	33	5.32	23.08	5.79
Hoflich	2015	30	54.1	14.6	31.1	2.4
Nagels	2011	15	53.27	6.71	30.53	1.4
Vernaleken	2013	10	46.8	16.6	30	0
Horacek	2010	20	38.35	14.82	0.65	1.26
Krystal	2006	31	40.2	21.21	29.2	0
Grent-‘t-Jong	2018	14	60.1	8.6	35.7	3.37
Mathalon	2014	9	45.7	10.8	30	0
Abdallah	2018	14	32.71	11.94	17.43	5.095
D'Souza	2012	32	57.97	15.11	30.56	2.84
Morgan	2011	16	11.06	4.89	7.06	0.25
Boeijinga	2007	12	23	6.92	19	2.08
Thiebes	2017	24	53.93	10.72	31.04	1.37
Dickerson	2010	93	35.2	5.75	30.47	0.85

eTable 2. Raw Data Used in Positive BPRS and PANSS Analysis for Healthy Participants

Author	Year	Sample Size	Ketamine mean	Ketamine S.D	Placebo mean	Placebo S.D
Kraguljac	2017	15	5.87	1.69	3	0
Anand	2000	16	8.5	2.42	4	0
Newcomer	1999	15	5	1.6	3	0
Krystal	1998	23	9.2	2.55	4.2	0.74
Breier	1997	17	9.2	3.2	4.4	1
Krystal	1999	20	7.3	0.68	4	0
Krystal	2003	26	8	3.88	3.9	0
Micallef	2002	8	6.7	4.8	4	0
Thiebes	2017	24	11.54	3.86	6.96	0.69
Powers	2015	19	12.8	4.14	7.08	0
Hoflich	2015	30	14.5	4.7	7.2	0.4
Nagels	2011	15	12.5	2.22	7.3	2.14
Vernaleken	2013	10	10.3	2.9	7	0
Krystal	2005	27	9.04	2.14	6.65	0.89
Krystal	2006	31	9.8	3.14	6.8	1.16
Kleinloog	2015	30	13	2.5	6.8	0.6
Grent-‘t-Jong	2018	14	7.2	1.87	4.1	0.37
D'Souza	2018	26	10.35	2.04	7.15	0.46
Driesen	2013	22	11.18	2.06	7.18	0.5
D'Souza	2012	32	16.25	4.69	7.47	0.8
Dickerson	2010	93	8.87	2.27	7.22	0.47

eTable 3. Raw Data Used in Negative BPRS and PANSS Analysis for Healthy Participants

Author	Year	Sample Size	Ketamine mean	Ketamine S.D	Placebo mean	Placebo S.D
Kraguljac	2017	15	6.87	1.96	3.13	0.35
Anand	2000	16	10.5	5.3	3.4	0.94
Krystal	1998	23	7.3	2.83	3.4	0.94
Krystal	1999	20	7.8	2	3.2	0
Krystal	2003	26	6.8	3	3.2	0
Duncan	2001	16	5.8	3	2.9	0.5
Micallef	2002	8	13.1	10.1	3	0
Malhotra	1997	16	6.5	2.4	3.5	0.8
Thiebes	2017	24	14.33	4.43	8.13	0.34
Powers	2015	19	9.77	2.6	7.21	1.18
Hoflich	2015	30	9.2	2.9	7.3	1
Nagels	2011	15	18.12	5	7.27	1.4
Vernaleken	2013	10	15	8.51	7	0
Krystal	2005	27	11.61	2.87	7.45	0.62
Krystal	2006	31	11.7	4.14	7.52	1.31
Kleinloog	2015	30	12	3.8	7.7	1
Grent-‘t-Jong	2018	14	13.5	3.74	8	2.24
Abdallah	2018	14	3.93	2.67	2.79	0.8
D'Souza	2018	26	8.54	1.27	7.65	0.94
Driesen	2013	22	8.68	2.1	7.41	0.91

D'Souza	2012	32	14.38	5.33	7.06	1.22
Dickerson	2010	93	7.87	1.41	7.24	0.6

eTable 4. Raw Data used in Total, Negative and Positive BPRS and PANSS Analysis for People With Schizophrenia

	n	**Placebo condition** Total: Positive: Negative Mean (S.D)	**Ketamine Condition** Total: Positive: Negative Mean (S.D)
Malhotra 1997[59]	13	31.9 (8.7)	40.1 (10.5)
Malhotra 1998[65]	18	NR: 8.6 (2.7): 7.6 (2.9)	NR:13.1 (4.0): 9.0 (4.1)
Lahti 2001 [20]	17	-0.9 (-3): 0.1 (0.8): 0.2 (0.8)	6.8 (-9): 3.3 (2.4): 1 (3.1)

NR: Not reported

eTable 5. Study Description, Ketamine Method, Placebo Condition, Symptoms (BPRS and PANSS), and Exclusion Criteria in Studies Examining Acute Ketamine Administration in Healthy Controls

Study	Blinded	Randomised	Ketamine method of administration/ dose/timing	Placebo condition	Symptoms (BPRS)	Exclusion Criteria
Kraguljac 2017 [66]	No	No	IV bolus of ketamine 0.27mg/kg over 10mins. Followed by continuous infusion (0.25mg/kg/h, flow rate of 0.01 ml/s). No information on length of infusion Time between placebo and ketamine test: same day	saline	Total Positive (2) Negative	Family history of psychosis, major medical or neurological disorder, prior exposure to ketamine, concurrent psychotropic medication use
Kort 2017 [49]	Double	Yes	IV bolus of ketamine 0.23mg/kg over 1min. Followed by 0.58 mg/kg/hour for 30mins. Followed by 0.29 mg/kg/hour for 50 mins. Time between placebo and ketamine test: 12.65+/-11.92 days Fasted prior to ketamine: yes	saline	Total	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
Duncan 2001 [50]	Double	Yes	IV ketamine 0.5mg/kg infused over 60mins Time between placebo and ketamine test: 8 days (range 4-21) Time of day ketamine given: morning Fasted prior to ketamine: yes	saline	Total Negative Timings: 50mins	Past or present psychiatric history, substance dependence, family history of psychosis, major medical or neurological disorder
Parwani 2005 [51]	Double	Yes	IV bolus ketamine 0.27 mg/kg over 10mins. Followed by 0.12 mg/kg over the remaining 50 mins Time between placebo and ketamine test: 11 days(range 1-75) Time of day ketamine given: morning Fasted prior to ketamine: yes	saline	Total Timing: 15 mins after infusion start	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder

Rowland 2005 [67]	Double	Yes	IV bolus of ketamine 0.27mg/kg over 10mins. Followed by 0.00225 mg/kg per min for up to 120mins Time between placebo and ketamine test: 7-14 days	saline	Total Timing: 45 mins after infusion start	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder
Abel 2003 [52]	Double	Yes	IV bolus of ketamine 0.23 mg/kg over 5mins. Followed by an infusion of 0.5mg/kg for 40 to 60 mins Time between placebo and ketamine test: >7 days	saline	Total Timing: 15 mins after infusion start	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder, prior exposure to ketamine, concurrent psychotropic medication use
Anand 2000[68]	Double	Yes	IV bolus of ketamine 0.26 mg/kg for 1 min. Followed by 0.65 mg/kg for 90mins infusion Time between placebo and ketamine test: 3-7 days	saline	Positive (1) Negative Timing: 5mins after infusion start	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
Krystal 1998 [69]	Double	Yes	IV bolus of ketamine 0.26mg/kg for 1 min. Followed IV infusion of 0.65 mg/kg for 60 mins Time between placebo and ketamine test: 3-7 days	saline	Positive (1) Negative Timing: positive symptoms 60 mins & negative symptoms 60 mins after infusion start	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder
Breier 1997 [70]	Double	Yes	IV bolus of ketamine 0.12 mg/kg. Followed by 0.65mg/kg constant infusion for 60mins Time between placebo and ketamine test: 7.8 (6.5) days	saline	Positive (1)	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder

van Berckel 1998 [57]	Double	Yes	IV ketamine 30ml/hr for 40 mins. Followed by 20ml/hr for 10mins. Followed by 10ml/h for 85 mins Time between placebo and ketamine test: > 7 days Time of day ketamine given: morning Fasted prior to ketamine: yes		Total Timing: 40mins after infusion start	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder
Malhotra 1997 [19]	Double	Yes	IV ketamine bolus of 0.12mg/kg. Followed by 0.65mg/kg of ketamine (max dose 58 mg) over one hour for a total dose of 0.77mg/kg/hr Time between placebo and ketamine test: >1 day Time of day ketamine given: morning Fasted prior to ketamine: yes	saline	Total Negative Timing: 55 mins after infusion start.	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder
Krystal 1999 [71]	Double	Yes	IV bolus of ketamine 0.26 mg/kg over 1 min. Followed infusion of 0.65 mg/kg for 60mins Time between placebo and ketamine test: 3-7 days	saline	Positive (1) Negative Timing: Positive symptoms 60mins & negative symptoms 60 mins post infusion start	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use

Krystal 2003 [72]	Double	Yes	IV infusion of 0.5mg/kg ketamine for 40 mins Time between placebo and ketamine test: 3-7 days Time of day ketamine given: morning Fasted prior to ketamine: yes	saline	Positive (1) Negative Timing: 80 mins after start of infusion	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
Micallef 2002 [73]	Double	Yes	IV ketamine 0.5 mg/kg infusion for 60 mins Time between placebo and ketamine test: 7 days	saline	Positive (1) Negative	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
Rowland 2010 [53]	Double	Yes	IV bolus of ketamine 0.2mg/kg over 10mins. Followed by maintenance dose of 0.4mg/kg/hr. No information on length. Time between placebo and ketamine test: >1 day Fasted prior to ketamine: yes	saline	Total	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, prior exposure to ketamine
Newcomer 1999 [74]	Double	Yes	IV bolus of 0.27 mg/kg of ketamine over 10mins. Followed by infusion of 0.00225 mg/kg/min. No information on the length of the infusion Time between placebo and ketamine test: 2.6 +/-1.1 days Time of day ketamine given: morning Fasted prior to ketamine: yes	saline	Total Positive (1) Timings: 30 mins after start of infusion	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder, prior exposure to ketamine

Stone 2011[75]	Double	Yes	IV bolus of ketamine at a rate of 0.23 mg/kg over 30s followed by an infusion of 0.65 mg/kg/h Time between placebo and ketamine test: >1 day	saline	Total	Major medical or neurological disorder, prior exposure to ketamine
Boeijinga 2007[28]	Double	Yes	IV bolus of ketamine at a rate of 0.081 mg/kg over 10 mins followed by 0.000675 infusion for 120 mins. Time between placebo and ketamine test: 7 days Fasted prior to ketamine: yes	saline	Total Timings: 30 mins after start of infusion	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
Passie 2003 [54]	Double	Yes	IV S-ketamine bolus 5mg over 5 mins. Followed by continuous infusion of 0.005mg/min/kg Time between placebo and ketamine test: >7 days Time of day ketamine given: afternoon	saline	Total	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder

Abdallah 2018 [76]	Single	No	IV ketamine bolus 0.23 mg/kg. Followed by continuous infusion of 0.58mg/kg over 75 mins. Time between placebo and ketamine test: >7 days Time of day ketamine given: afternoon	saline	Total Negative Timings: 120 mins after start of infusion	Past or present psychiatric history, recent substance abuse, family history of psychosis, major medical or neurological disorder
Morgan 2011[77]	Double	no	IV ketamine with targeted plasma concentration of 100 ng/ml for 60 mins and then 200 ng/ml for further 60mins	saline	Total	Past or present psychiatric history, recent substance misuse
Horacek 2010 [55]	Double	Yes	IV bolus of 0.27 mg/kg of ketamine over 10mins. Followed by infusion of 0.27mg/kg for 20mins. Time between placebo and ketamine test: > 14 days	saline	Total Timing: 30mins after start of infusion	Past or present psychiatric history, recent substance misuse, family history of psychosis
Thiebes 2017[78]	Single	Yes	IV bolus of 10 mg of s-ketamine over 5 mins. Followed by infusion of 0.006 mg/kg/min. As ketamine plasma levels slowly increase with continuous infusion, the dosage was reduced by 10% every 10 minutes, for 75 mins. Time between placebo and ketamine test: > 7 days	saline	Total Positive Negative	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder

Powers 2015[79]	No	No	IV bolus of 0.23 mg/kg of ketamine over 1 min. Followed by infusion of 0.58mg/kg/h for 75 mins.	saline	Positive Negative	Past or present psychiatric history, substance dependence, family history of psychosis, major medical or neurological disorder
Mathalon 2014 [80]	Double	Yes	IV bolus of 0.26 mg/kg of ketamine over 1 min. Followed by infusion of 0.65mg/kg/h for 120 mins. Time between placebo and ketamine test: >3 days Fasted prior to ketamine: yes	saline	Total Timing: 1min	Past or present psychiatric history, substance misuse, family history of psychosis, major medical or neurological disorder
Hoflich 2015[81]	Double	Yes	IV bolus of 0.11 mg/kg of s-ketamine over 1 min. Followed by infusion of 0.12 mg/kg for 19 mins. Fasted prior to ketamine: yes	saline	Total Positive Negative	Past or present psychiatric history, substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
Nagels 2011[82]	Double	Yes	IV bolus of 8mg mg/kg of s-ketamine over 5 min. Followed by infusion of 0.01 mg/kg/min for 60 mins.	saline	Total Positive Negative	Past or present psychiatric history, substance misuse, family history of psychosis, major medical or neurological disorder
Driesen 2013 [83]	No	No	IV bolus of 0.23mg/kg of ketamine over 1 min. Followed by infusion of 0.58mg/kg/min for 45 mins. Time between placebo and ketamine test: <1 day	saline	Positive Negative Timing 45mins	Past or present psychiatric history, family history of psychosis, major medical or neurological disorder
Vernaleken 2013 [84]	Single	Yes	IV bolus of 8mg of s-ketamine over 5 min. Followed by infusion of 0.01 mg/kg/min for 60 mins. Time between placebo and ketamine test: > 7 days	saline	Total Positive Negative	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder, concurrent psychotropic medication use

Krystal 2005 [85]	Double	Yes	IV bolus of 0.23mg/kg of ketamine over 1 min. Followed by infusion of 0.5 mg/kg for 60 mins. Time between placebo and ketamine test: >1 day	saline	Positive Negative Timing: Positive symptoms 60 mins & negative symptoms 60 mins.	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
Krystal 2006 [86]	Double	Yes	IV bolus of 0.23mg/kg of ketamine over 1 min. Followed by infusion of 0.58 mg/kg/h for 60 mins. Time between placebo and ketamine test: > 1 day Time of day ketamine given: morning Fasted prior to ketamine: yes	saline	Total Positive Negative Timing: Total symptoms 80 mins Positive symptoms 80 mins & negative symptoms 10 mins.	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder
Kleinloog 2015 [87]	Double	Yes	IV s-ketamine with targeted plasma concentration of 240 ng/ml (bolus +continuous design used) Time between placebo and ketamine test: > 1 day	saline	Total Positive Negative	Past or present psychiatric history, substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use
D'Souza 2012[88]	Double	Yes	IV bolus of 0.23mg/kg of ketamine over 1 min. Followed by infusion of 0.58mg/kg for 30 mins. Followed by 0.29 mg/kg/hour for 64 mins. Time between placebo and ketamine test: >2 days Fasted prior to ketamine: yes	saline	Total Positive Negative	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder, concurrent psychotropic medication use

Grent-'t-Jong 2018 [89]	Single	Yes	IV bolus of 10mg of s-ketamine. Followed by infusion of 0.006 mg/kg/min for 45 mins.	saline	Total Negative Positive	Major medical or neurological disorder
D'Souza 2018 [90]	NR	No	IV bolus of 0.23 mg/kg of ketamine over 1 min. Followed by infusion of 0.58 mg/kg/hour for 45 mins. Time between placebo and ketamine test: <1 day	saline	Total Negative Positive	Past or present psychiatric history, recent substance misuse, family history of psychosis, major medical or neurological disorder
Dickerson 2010 [91]	Single	Yes	IV bolus of 0.23 mg/kg of ketamine over 1 min. Followed by infusion of 0.58 mg/kg/hour for 45 mins. Time between placebo and ketamine test: >3 days Fasted prior to ketamine: yes	saline	Total Negative Positive	Past or present psychiatric history, recent substance misuse, major medical or neurological disorder

BPRS Positive symptoms (1): conceptual disorganisation, suspiciousness, hallucinatory behaviour, unusual thought content
BPRS Positive symptoms (2): conceptual disorganisation, hallucinatory behaviour, unusual thought content
BPRS Negative symptoms: Blunted affect, emotional withdrawal, motor retardation

eTable 6. Study Description, Ketamine Administration Method, Placebo Condition, Symptoms (BPRS), and Exclusion Criteria in Studies Examining Acute Ketamine Administration to Patients With Schizophrenia

Study	M:F	Diagnosis	Medication	Blinding	Randomised	Ketamine method of administration/ dose/timing	Placebo condition	Symptoms (BPRS)	Exclusion
Malhotra 1998 [92]	13:5	Schizophrenia Schizoaffective disorder	Fluphenazine (3) Clozapine (4) Antipsychotic free (11)	Double	yes	IV bolus of 0.12mg/kg of ketamine. Followed by 0.65mg/kg infusion over 60 mins. Time between placebo and ketamine test: >1 day		Positive (1) Negative Timing: 35 mins after start of infusion	Medical illness, current alcohol or drug abuse
Malhotra 1997 [59]	10:3	Schizophrenia Schizoaffective disorder	Unmedicated for two weeks (12) Medication naïve (1)	Double	yes	IV bolus of 0.12mg/kg of ketamine. Followed by 0.65mg/kg of ketamine (max dose 58 mg) over 60mins for a total dose of 0.77mg/kg/hr Time between placebo and ketamine test: >1 day Time of day ketamine given: morning Fasted prior to ketamine: yes	saline	Total Timing: 55 mins	Medical illness, current alcohol or drug abuse
Lahti 2001 [20]	11:6	Schizophrenia	Haloperidol 0.3mg/kg/day	Double	yes	IV bolus of 0.3mg/kg of ketamine for 60 secs Time between placebo and ketamine test: >1 day		Total Positive (2) Negative Timing: 20 mins after infusion start.	Medical illness, no current alcohol or drug abuse

Positive symptoms (1): conceptual disorganisation, suspiciousness, hallucinatory behaviour, unusual thought content
Positive symptoms (2): conceptual disorganisation, hallucinatory behaviour, unusual thought content
Negative symptoms: Blunted affect, emotional withdrawal, motor retardation

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