Supplementary material

**Table S1.** Articles excluded after full-text revision.

|  |  |  |
| --- | --- | --- |
| **Reason for exclusion** | **Explication** | **Studies excluded** |
| *No original data* | The studies provide only data referring to neuroanatomy, the sample has been manipulated or it is a summary of a conference, for example | **Clark, L.** (2001). A neuropsychological investigation of prefrontal cortex involvement in acute mania  **Gollier-Briant, F.** (2008). The neural correlates of decision-making in bipolar disorder: An fMRI study  **Martino, D.** (2014). A comparison of decision making in patients with bipolar I disorder and schizophrenia  **Roiser, J.** (2009). The effect of positive mood induction on emotional processing in euthymic individuals with bipolar disorder and controls  **Trost, S.** (2014). Disturbed anterior prefrontal control of the mesolimbic reward system and increased impulsivity in bipolar disorder |
| *No behavioural measures* | Studies don’t use a behavioural paradigm to assess the cognitive domains | **Molz, A.** (2013). Aggression and impulsivity as predictors of stress generation in bipolar spectrum disorders  **Muhtadie, L.** (2014). A profile approach to impulsivity in bipolar disorder: the key role of strong emotions  **Perroud, N.** (2011). Impulsivity, aggression and suicidal behavior in unipolar and bipolar disorders |
| *Non-standardized test* | Studies employ unusual behavioral paradigms | **Henry, B.** (2013). Inhibitory deficits in euthymic bipolar disorder patients assessed in the human behavioral pattern monitor  **Mason, L.** (2014). Decision-making and trait impulsivity in bipolar disorder are associated with reduced prefrontal regulation of striatal reward valuation  **Mason, L.** (2016). Attentional bias predicts increased reward salience and risk taking in bipolar disorder  **Welander-Vatn, A.S.** (2009). No altered dorsal anterior cingulated activation in bipolar II disorder patients during a Go/No-go task: an fMRI study |
| *No BD diagnostic* | The study sample isn’t diagnosed with Bipolar Disorder | **Mason, L.** (2012). I want it now! Neural correlates of hypersensitivity to immediate reward in hypomania |
| *Duplicated sample* | After careful review of the studies the authors considered that the samples came from the same centre, had an N, a very similar sex and age distribution. As a precaution, we decided to exclude them to avoid possible duplicated data | **Adida, M.** (2008). Lack of insight may predict impaired decision making in manic patients  **Adida, M.** (2015). Lithium might be associated with better decision-making performance in euthymic bipolar patients  **Bauer, I.** (2018). Increased reward-oriented impulsivity in older bipolar patients: A preliminary study |
|  |  | **Strakowski, S.** (2008). MRI brain activation in first-episode bipolar mania during a response inhibition task  **Strakowski, S.** (2009). Characterizing impulsivity in mania  **Swann, A.** (2003). Impulsivity and phase of illness in bipolar disorder  **Swann, A.** (2011). Interacting mechanisms of impulsivity in bipolar disorder and antisocial personality disorder  **Swann, A.** (2013). Pre-attentive information processing and impulsivity in bipolar disorder |
| *No data for Meta-Analysis* | The studies don’t provide the necessary data to perform the meta-analysis | **Cotrena, C.** (2016). Executive function impairments in depression and bipolar disorder: association with functional impairment and quality of life  **Ono, Y.** (2015). Reduced prefrontal activation during performance of the Iowa Gambling Task in patients with bipolar disorder  **Minassian, A.** (2004). Increased sensitivity to error during decision-making in bipolar disorder patients with acute mania  **Powers, R.** (2013). Impulsivity in bipolar disorder: relationships with neurocognitive dysfunction and substance use history  **Saunders, K.** (2015). Insensitivity to the magnitude of potential gains or losses when making risky choices: women with borderline personality disorder compared with bipolar disorder and controls  **Strasser, E.** (2016). Behavioral measures and self-report of impulsivity in bipolar disorder: no association between Stroop test and Barratt Impulsiveness Scale  **Swann, A.** (2001). Measurement of inter-episode impulsivity in bipolar disorder  **Yechiam, E.** (2008). Decision making in bipolar disorder: A cognitive modeling approach |
| *Outcome measure not valid* | Outcome measure is not valid to assess the cognitive domain. | **Chandler, R.** (2009). Altered risk-aversion and risk-seeking behavior in bipolar disorder |

**Table S2**. Description of the information collected from the studies.

|  |  |  |
| --- | --- | --- |
| **Variable** | **Description** | **Categories** |
| FIRST AUTHOR | First Author of the publication. |  |
| YEAR-PUBLICATION | Year which the article was published. |  |
| MEAN AGE | Mean age of the study population. |  |
| SAMPLE | Number of individuals included in the study | - BD-I  - BD-II |
| PHASE OF ILLNES | Phase of bipolar disorder at the time of the study. | - Mania  - Depression  - Euthymia  - Hypomania  - Mixed epidose |
| NEUROCOGNITIVE TEST | Instrument used to assess the cognitive domain. |  |
| NEUROCOGNITIVE OUTCOME | Cognitive domain measured in the study. | - Impulsivity: Response inhibition, Delay aversion or Inattention.  - Decision-making  - Risk taking |
| RESULTS | Summary of the results of the study. |  |
| AGE RANGE | Age Range of the population in the study. |  |
| GENDER | Gender of the study population expressed as a percentage. | - Male  - Female |
| STUDY DESIGN | Whether the study is cross-sectional or longitudinal. | - Cross-sectional  - Longitudinal |
| NEUROIMAGING TEST | Use of a neuroimaging test during the study. | - Yes  - No |
| MATCHING | Way in which the population was matched with healthy controls. | - Depending of study variables  - Not matched |
| QUALITY OF STUDY | Indicates the quality range of the study through the Newcastle-Ottawa Scale (NOS). | 0-9 |
| FUNDING | Sources of funding for the study or other support. | - Yes  - No |

BD-I, Bipolar disorder type I; BD-II, Bipolar disorder type II.

**Table S3**. Quality Reporting Scale (The Newcastle-Ottawa Scale).\*†

|  |  |
| --- | --- |
| **Items for case controls studies** | **Quality Score** |
| **SELECTION** | |
| 1. Is the case definition adequate?   1. Yes, with independent validation 2. Yes, eg record linkage or based on self-reports 3. No description | 1  0  0 |
| 2. Representativeness of the cases   1. Consecutive or obviously representative series of cases 2. Potential for selection biases or not stated | 1  0 |
| 3. Selection of Controls   1. Community controls 2. Hospital controls 3. No description | 1  0  0 |
| 4. Definition of Controls   1. No history of disease (endpoint) 2. No description of source | 1  0 |
| **COMPARABILITY** | |
| 1. Comparability of cases and controls on the basis of the design or analysis   1. Study controls for\_\_\_\_\_\_\_\_\_\_\_ (Select the most important factor) 2. Study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor) | 1  1 |
| **EXPOSURE** | |
| 1. Ascertainment of exposure   1. Secure record (eg surgical records) 2. Structured interview where blind to case/control status 3. Interview not blinded to case/control status 4. Written self-report or medical record only 5. No description | 1  1  0  0  0 |
| 2. Same method of ascertainment for cases and controls   1. Yes 2. b) No | 1  0 |
| 3. Non-Response rate   1. Same rate for both groups 2. Non respondents described 3. Rate different and no designation | 1  0  0 |

\* Range = 0-9; Maximum score in each section: 4, 2 and 3, respectively; Quality: Low (< 5 score); Medium (5-6 score); High (≥ 7 score).

†Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. & Tugwell, P. (2014). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Health Research Institute. http://www.ohri.ca/programs/clinical\_epidemiology/oxford.asp

**Table S4**. Characteristics and quality assessment of the studies selected.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author,  year-pub | Age range | Gender | Study design | Neuroimaging test | Matching | Quality of study | Funding | Neurocognitive test |
| Adida et al. (2011) | 18 – 65  19 – 64 | BD patients  41.3% M, 58.7% F  Controls  50% M, 50% F | Cross-sectional study | No | Age, level of education, NART (Z score) and sex ratio | 8 | Yes | Iowa Gambling Task (IGT) |
| Ahn et al. (2011) | Not specified | BD patients  45.5% M, 54.5% F  Controls  40% M, 60% F | Cross-sectional study | No | Not matched | 6 | Yes | Delay Discounting Task |
| Bauer et al. (2017) | Not specified | BD patients  28.8% M, 71.2% F  Controls  34.4% M, 65.6% F | Cross-sectional study | No | Not matched | 6 | Yes | Affective Go/No-Go task (AGN)  Cambridge Gambling Task (CGT) |
| Bersani et al. (2016) | Not specified | BD patients  60% M, 40% F  Controls  46.7% M, 53.3% F | Cross-sectional study | No | Age, gender, educational level and intelligence | 8 | Not specified | Stop Signal Task (SST) |
| Brambilla et al. (2013) | 18 – 65 | BD patients  52.9% M, 47.1% F  Controls  50.7% M, 49.3% F | Cross-sectional study | No | Age, sex and IQ | 8 | Yes | Iowa Gambling Task (IGT) |
| Cheema et al. (2015) | 18 – 60 | BD patients  61.9% M, 38.1% F  Controls  52.2% M, 47.8% F | Cross-sectional study | No | Age and gender ratio | 8 | Yes | Emotional Go/No-Go Task |
| Duek et al. (2014) | 18 – 65 | BD patients  55% M, 45% F  Controls  56.1% M, 43.9% F | Cross-sectional study | No | Age and education | 8 | Not specified | Single Key Impulsivity Paradigm (SKIP) |
| Edge et al. (2013) | 18 – 65 | BD patients  35% M, 65% F  Controls  41% M, 59% F | Cross-sectional study | No | Not matched | 6 | Yes | Iowa Gambling Task (IGT) |
| Fleck et al. (2011) | Not specified | BD patients  38.9% M, 61.1% F  Controls  20% M, 80% F | Cross-sectional study | Yes | Age, sex, race, education years | 8 | Yes | Go/No-Go Task |
| Hidiroğlu et al. (2013) | 21 – 59  20 – 69  22 – 59 | BD patients  36.7% M, 63.3% F  BD-Relatives  32% M, 68% F  Controls  36.7% M, 63.3% F | Cross-sectional study | No | Sex, age and educationally | 8 | Yes | Balloon Analogue Risk Task (BART) |
| Holmes et al. (2009) | 21 – 63  21 – 60 | BD patients  38.2% M, 61.8% F  Controls  44% M, 56% F | Cross-sectional study | No | Age, years of education, race, full scale IQ | 6 | Yes | Balloon Analogue Risk Task (BART) |
| Hummer et al. (2013) | 18 – 60 | BD patients  36.5% M, 63.5% F  Controls  36.6% M, 63.3% F | Cross-sectional study | Yes | Age and gender | 8 | Yes | Picture of Facial Affect (Go/No-Go Task) |
| Ibañez et al. (2012) | 18 – 64 | BD patients  61.5% M, 38.5% F  Controls  64% M, 36% F | Cross-sectional study | Yes | Sex, age, handedness and years of education | 8 | Not specified | Iowa Gambling Task (IGT) |
| Jogia et al. (2012) | 18-63 | BD patients  47.2% M, 52.8% F  Controls  56.7% M, 43.3% F | Cross-sectional study | Yes | Age, IQ and BPRS | 7 | Yes | Iowa Gambling Task (IGT) |
| Kaladjian et al. (2009) | Not specified | BD patients  50% M, 50% F  Controls  50% M, 50% F | Cross-sectional study | Yes | Sex, age, handedness, estimated premorbid IQ and level of education | 7 | Not specified | Go/No-Go Task |
| Kopf et al. (2018) | Not specified | BD patients  52.8% M, 47.2% F  Remitted patients  66.7% M, 33.3% F  Controls  33.3% M, 66.7% F | Cross-sectional and longitudinal study | Yes | Age, sex and performance on the multiple-choice word test  (MWT-B) | 8 | Yes | Combined Stop-Signal-Go/No-Go Task |
| Linke et al. (2013) | 18 – 65 | BD I patients  42.1% M, 57.9% F  BD-Relatives  50% M, 50% F  Controls  42.1% M, 57.9% F | Cross-sectional study | Yes | Age and gender | 9 | Yes | Cambridge Gambling Task (CGT) |
| Malloy-Diniz et al. (2011) | Not specified | BD patients  30.5% M, 69.5% F  Controls  43.6% M, 56.4% F | Cross-sectional study | Yes | Not matched | 6 | Yes | Continuous Performance Test (CPT-II)  Iowa Gambling Task (IGT) |
| Martino et al. (2011) | 18-60 | BD- I  39.4% M, 60.6%F  BD-II  21.5% M, 78.5% F  Controls  35.3 M, 64.7% F | Cross-sectional study | No | Age and years of education | 7 | Yes | Iowa Gambling Task (IGT) |
| Mazzola-Pomietto et al. (2009) | Not specified | BD patients  37.5% M, 62.5% F  Controls  37.5 % M, 62.5%F | Cross-sectional study | Yes | Sex, age and handedness | 7 | Yes | Go/No-Go Task |
| Moraes et al. (2013) | Not specified | BD patients  31.6% M, 68.4% F  Controls  36.5% M, 63.5% F | Cross-sectional study | No | Not matched | 6 | Not specified | Continuous Performance Test II (CPT-II)  Iowa Gambling Task (IGT) |
| Murphy et al. (2001) | Not specified | BD patients  44.5% M, 55.5% F  Controls  46.2% M, 53.8% F | Cross-sectional study | No | Age, sex and NART-IQ | 8 | Yes | Decision-making task |
| Okasha et al. (2014) | 18-50 | BD patients  50% M, 50% F  Controls  50% M, 50% F | Cross-sectional study | No | Age, gender and educational level | 7 | No | Continuous Performance Test (CPT) |
| Reddy et al. (2014) | Not specified | BD patients  54.4% M, 45.6% F  Controls  55.6% M, 44.4% F | Cross-sectional study | No | Not matched | 6 | Yes | Balloon Analogue Risk Task (BART) |
| Rubinsztein et al. (2006) | 18-60 | Not specified | Cross-sectional study | No | Gender, IQ and age | 7 | Yes | Decision-making task |
| Scholz et al. (2016) | Not specified | BD patients  58.3% M, 41.7% F  Controls  58.3% M, 41.7% F | Cross-sectional study | Yes | Age, gender and years of education | 8 | Yes | Cambridge Gambling Task (CGT) |
| Strakowski et al. (2010) | 18-50 | BD patients  46% M, 54% F  Controls  40% M, 60% F | Longitudinal study | No | Demographic variables | 7 | Yes | Logan Stop-Signal Task (SST)  Delayed Reward Task (DRT)  Degraded Stimulus version of the CPT (DSCPT) |
| Swann et al. (2009) | Not specified | BD patients  43.7% M, 56.3% F  Controls  42.9% M, 57.1% F | Cross-sectional study | No | Not matched | 5 | Yes | Immediate Memory Task (IMT)  Single Key Impulsivity Paradigm (SKIP) |
| Tavares et al. (2007) | 18-59 | BD patients  29.4% M, 70.6% F  Controls  28% M, 72% F | Cross-sectional study | No | Age and IQ | 7 | Yes | Cambridge Gamble Task (CGT) |
| van Enkhuizen et al. (2014) | 18-55 | BD patients  56.3% M, 43.7% F  Controls  29.4% M, 70.6% F | Cross-sectional study | No | Age, gender, education, and ethnicity | 8 | Yes | Iowa Gambling Task (IGT) |

BD, Bipolar disorder; M, Males; F, Females; NART, National Adult Reading Test; IQ, Intelligence Quotient; BPRS, Brief Psychiatric Rating Scale.

**Table S5**. Paradigms used to assess impulsivity, decision-making and risk behavior.

|  |  |  |
| --- | --- | --- |
| **Cognitive Domain** | **Paradigms** | **Score** |
| **Impulsivity** |  |  |
| *Response Inhibition* | Affective Go/No-Go task (AGN)  Emotional Go/No-Go task  Go/No-Go task  Picture of Facial Affect  Combined Stop-Signal-Go/No-Go Task  Stop Signal Task (SST)  Immediate Memory Task (IMT)  Continuous Performance Test (CPT)  Continuous Performance Test II (CPT-II) | Commission negative  Commission errors total  Proportion commission errors  Letter No-Go: No-Go trials  SSRT (ms)  SSRT (ms)  Commission errors  Commission errors  Commission errors |
| *Delay of Gratification* | Delay Discounting Task  Cambridge Gambling Task (CGT)  Delayed Reward Task (DRT)  Single Key Impulsivity Paradigm (SKIP) | Delay discounting choice behavior  Delay aversion  % IMP  Total responses (Number of presses) |
| *Inattention* | Continuous Performance Test (CPT)  Continuous Performance Test II (CPT-II)  Degraded Stimulus version of the CPT (DSCPT) | Omission errors  Omission errors  B” |
| **Decision-making** | Iowa Gambling Task (IGT)  Decision-making task  Cambridge Gambling Task (CGT) | Net score  Quality of decision making  Quality of decision making |
| **Risk behavior** | Cambridge Gambling Task (CGT)  Balloon Analogue Risk Task (BART) | Risk taking  Adjustment scores (Bart pumps) |

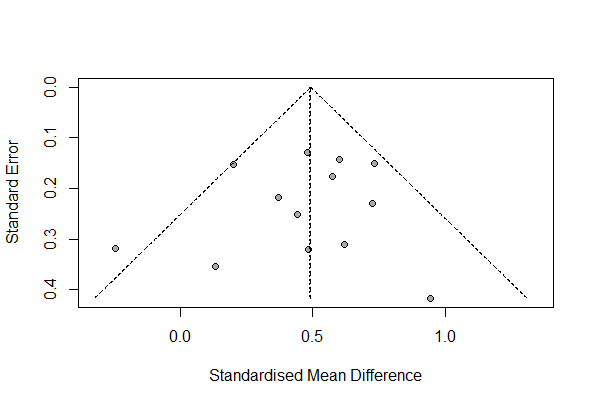
**Table S6.** Summary of the meta-analysis results.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Studies** | **Patients** | **Controls** | **ES**\* | **95% CI** | ***Z***† | ***p*** |
| Response inhibition complete | 13 | 869 | 595 | 0.49 | 0.38/0.60 | 8.92 | <0.0001 |
| Response inhibition euthymic | 7 | 335 | 327 | 0.59 | 0.43/0.75 | 7.23 | <0.0001 |
| Response inhibition depressed | 3 | 84 | 70 | 0.48 | 0.16/0.81 | 2.92 | 0.0035 |
| Response inhibition manic | 3 | 154 | 94 | 0.47 | 0.21/0.74 | 3.49 | 0.0005 |
| Response inhibition BD I - euthymic | 3 | 71 | 58 | 0.29 | -0.07/0.65 | 1.59 | 0.1121 |
| Response inhibition without CPT | 10 | 619 | 356 | 0.40 | 0.26/0.53 | 5.84 | <0.0001 |
| Delay of gratification | 5 | 466 | 283 | 0.54 | 0.39/0.70 | 6.97 | <0.0001 |
| Delay of gratification without CGT | 4 | 282 | 190 | 0.65 | 0.46/0.84 | 6.60 | <0.0001 |
| Inattention | 4 | 358 | 287 | 0.49 | 0.33/0.65 | 5.92 | <0.0001 |
| Decision making complete | 13 | 875 | 821 | 0.61 | -0.93/-0.28 | -3.68 | 0.0002 |
| Decision making euthymic | 8 | 502 | 634 | -0.39 | -0.51/-0.27 | -6.39 | <0.0001 |
| Decision making depressed | 3 | 73 | 201 | -0.92 | -2.99/1.15 | -0.87 | 0.3828 |
| Decision making manic | 3 | 79 | 193 | -1.35 | -2.43/-0.27 | -2.45 | 0.0143 |
| Decision making BD I – euthymic | 5 | 299 | 400 | -0.25 | -0.41/-0.10 | -3.22 | 0.0013 |
| Decision making Iowa Gambling Task | 9 | 632 | 651 | -0.43 | -0.55/-0.32 | -7.49 | <0.0001 |
| Risk taking complete | 6 | 380 | 227 | 0.41 | -0.02/0.84 | -1.88 | 0.0598 |
| Risk taking BD I – euthymic | 3 | 73 | 73 | 0.92 | 0.57/1.26 | 5.24 | <0.0001 |
| Risk taking Cambridge Gambling Task | 3 | 227 | 136 | 0.41 | -0.22/1.04 | 1.28 | 0.1992 |
| Risk taking Balloon Analogue Risk Task | 3 | 153 | 91 | 0.43 | -0.35/1.20 | 1.08 | 0.2799 |

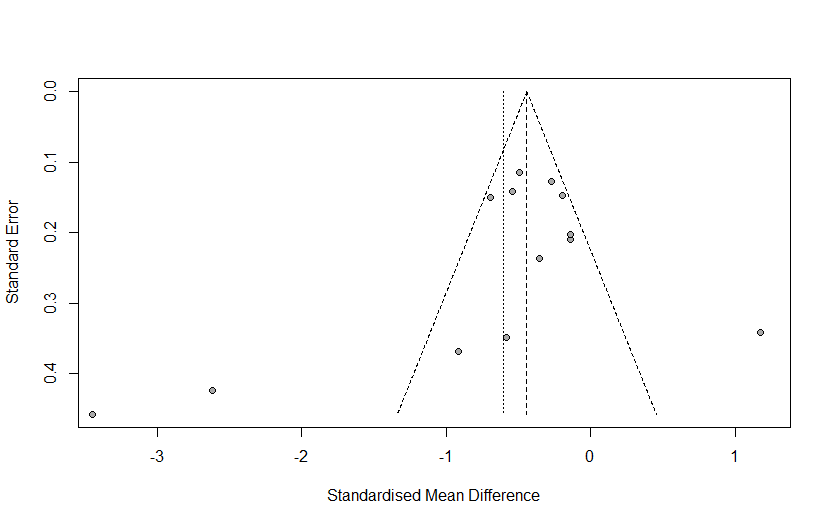
\*Effect Size

†Test of significance of effect size

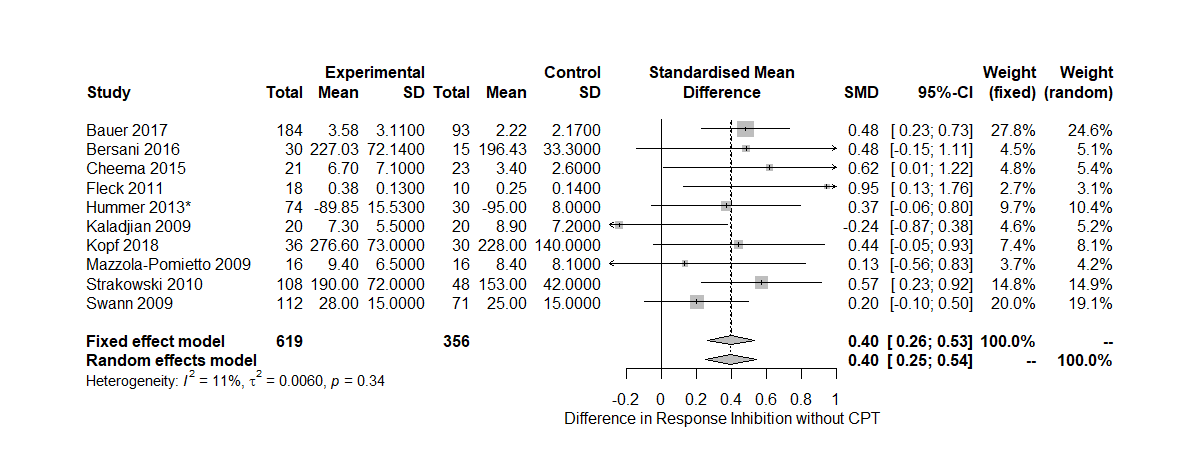
1. **Response inhibition**



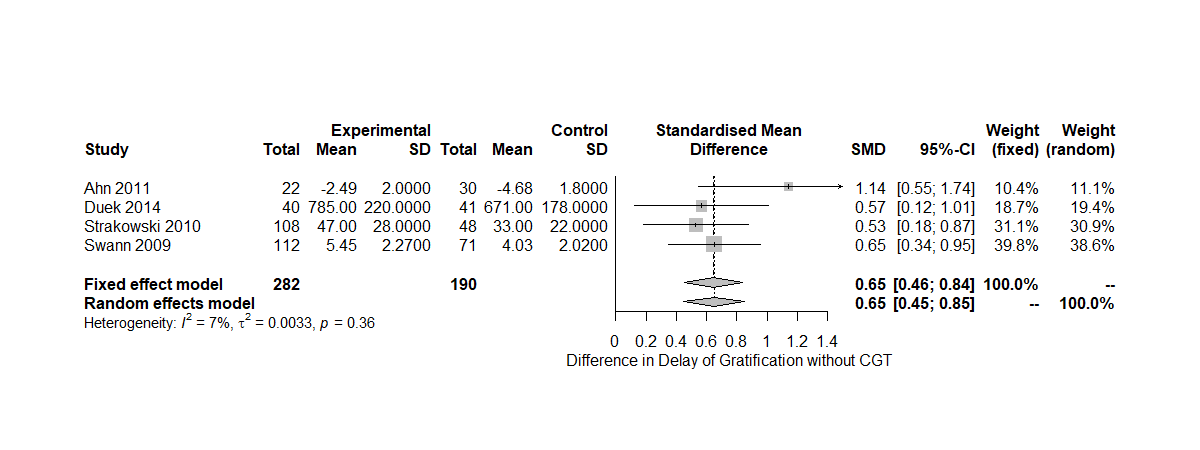
1. **Decision-making**



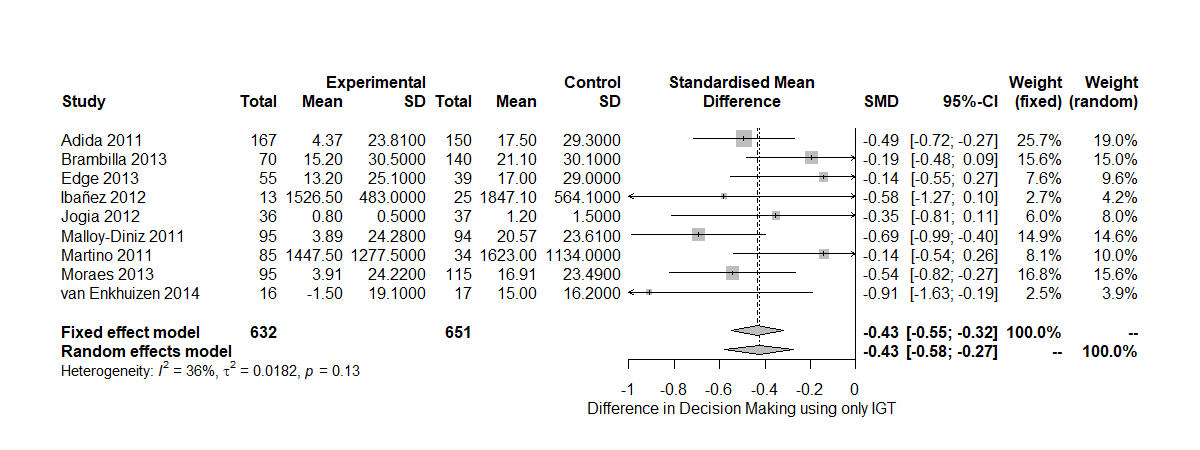
**Figure S1.** Funnel plots. (*a*) Response inhibition. Rank correlation test of funnel plot asymmetry (p=0.6255). Egger test of funnel plot asymmetry (p= 0.6058). (*b*) Decision-making. Rank correlation test of funnel plot asymmetry (p=0.1431). Egger test of funnel plot asymmetry (p= 0.2454).



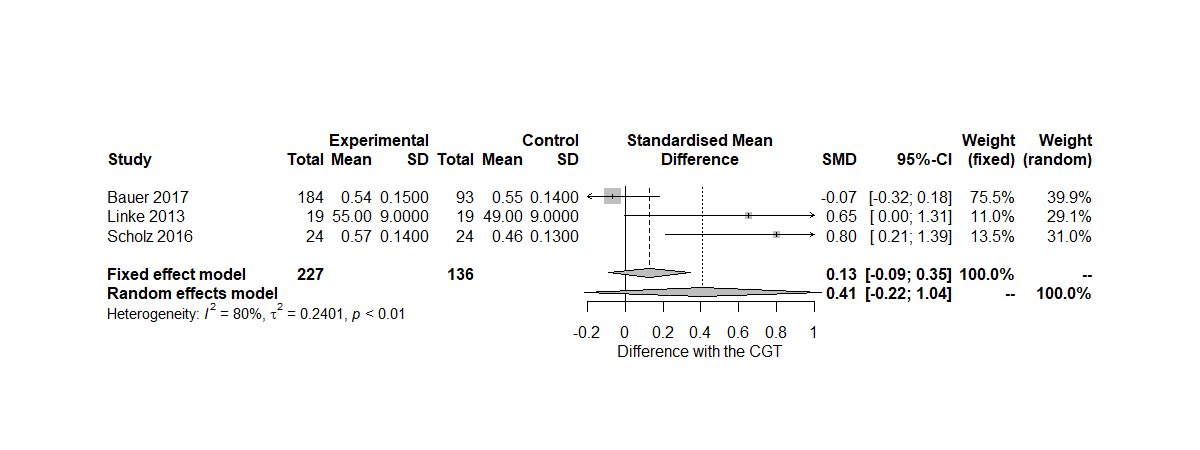
**Figure S2.** Forest plots of response inhibition without Continuous Performance Test.

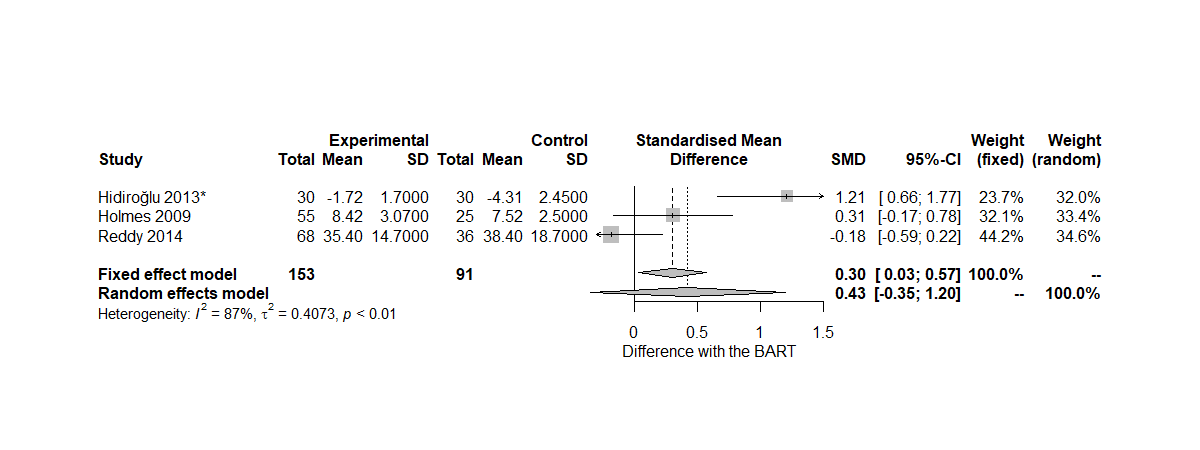


**Figure S3.** Forest plots of delay of gratification without Cambridge Gambling Task.



**Figure S4.** Forest plots of decision-making behavior using only Iowa Gambling Task.





**Figure S5.** Forest plots of risk-taking behavior using the Balloon Analogue Risk Task and the Cambridge Gambling Task.