Supplemental Materials

*Distinct neural effects of psychological therapy and antidepressant medication on the brain’s affect circuitry: a synthesis across three meta-analyses*

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*Inclusion criteria and procedure for synthesis of meta-analyses*

For both antidepressant medication (ADM)1 and psychological therapy (PT)2 meta-analyses, we ran an activation likelihood estimation (ALE) analysis on the following subsets of the original data:

From the PT meta-analysis, we included all pre- versus post-treatment studies reporting at least one coordinate from the original meta-analysis (K=17) (ALE analysis does not incorporate studies with no findings). To ensure this meta-analysis had sufficient and comparable statistical power for the contrast analysis with ADM, we did not exclude the four resting-state studies in the original meta-analysis. All other studies in both ADM and PT meta-analyses were task-based (see Table S1 for task type and contrast, imaging, and intervention type).

From the ADM meta-analysis, we included studies in patients reporting the effects of a course of antidepressant treatment (i.e., not those reporting results following a single dose of antidepressant administration, nor those conducted in healthy controls). If a study reported more than one post-treatment time, we included only the contrast at the later date (e.g. 16 weeks rather than 8 weeks); if a study reported more than one contrast (e.g., sad>happy and sad>neutral activation), we included only the first contrast listed in the data file. ADM meta-analyses included results from either within-subject analyses (pre- versus post-antidepressant treatment) or group-by-time interactions from mixed-design studies (K=24).

The contrasts were largely comparable between ADM and PT meta-analyses, with the vast majority reporting negative emotion valence contrasts (see Table S1 for specific contrasts). However, an important limitation of their comparability was four resting-state studies included in the psychological therapy meta-analysis. These four studies were included in the original meta-analysis for reasons of statistical power; without these four studies, the meta-analysis would be considered underpowered according to field-wide guidelines3. Therefore, we elected to include these studies with the caveat that it slightly diminishes the comparability of the samples.

After performing a standard ALE meta-analysis4–6 of PT and ADM data separately (to acquire a family-wise error (FWE) cluster-corrected map of convergence of changes following antidepressant treatment), we ran a conjunction analysis47 between the ADM and PT maps.

To compare PT and ADM effects with established ‘affect circuitry’ in the brain, we first extracted contrasts from a large database of affective task-based neuroimaging studies built for a previous meta-analysis8. The ‘affect circuitry’ studies we included represented a subset of the original database: we included only whole-brain (not region of interest [ROI]) results for valenced affect stimuli contrasted with a neutral emotion baseline. This produced 3867 foci from 216 experiments. After performing a standard ALE meta-analysis4–6 of the affect data (to acquire a FWE cluster-corrected map of convergence of affect-related activation), we ran a conjunction analysis with each equivalent map obtained from the ADM and PT meta-analyses above.

Note that the ALE algorithm compares the convergence of reported coordinates with those expected under random spatial association and tests for above-chance clustering using random-effects inference; foci are treated as three-dimensional Gaussian probability distributions centred on the coordinates and scaled according to sample size4–6. All three meta-analysis maps were thresholded at a cluster-level family-wise- error (FWE)-corrected threshold of *p*<0.05 (cluster-forming threshold at *p*<0.001; 1000 threshold permutations). The three conjunction analyses run were all set at a minimum volume of 50mm3 (*p*=0.05, 1000 *p*-value permutations), although we additionally verified the absence of any convergence between PT and ADM effects in an uncorrected *p*<0.001 conjunction analysis.

We list all study details in Table S1, including the time from pre- to post-treatment scan, which differed between ADM and PT (median 56 and 84 days, respectively; non-parametric Mann-Whitney U test *p*<0.001).

Our FWE-corrected results for all conjunction and contrast meta-analyses can be found in **Table S2** (*Convergence and divergence of neural changes following antidepressant medication (ADM) and psychological therapy (PT) for affective disorders*).

**Table S1. Details of studies included in PT and ADM contrast (N=613)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author | Year | Diagnosis | Intervention | N patients | Task | Contrast | Imaging | Time |
| Anand9 | 2007 | MDD | SSRI | 12 | emotion | negative emotion>fixation | fMRI | 42 |
| Arnone10 | 2012 | social phobia | SSRI | 30 | emotion | sad>neutral | fMRI | 56 |
| Aupperle11 | 2013 | PTSD | CBT (CTT) | 14 | emotion | negative>positive | fMRI | 28 |
| Benedetti12 | 2009 | MDD | SNRI | 8 | emotion | negative>positive | fMRI | 21 |
| Cornelius13 | 2010 | MDD | SSRI | 6 | emotion | fear>shape | fMRI | 56 |
| Davidson14 | 2003 | MDD | SNRI | 12 | emotion | negative>neutral | fMRI | 56 |
| Fales15 | 2009 | MDD | SSRI | 23 | emotion | fear>neutral | fMRI | 28 |
| Felmingham16 | 2007 | PTSD | CBT | 8 | emotion | fearful>neutral | fMRI | 56 |
| Frodl17 | 2011 | MDD | SNRI | 11 | emotion | sad>shapes | fMRI | 7 |
| Fu18 | 2004 | MDD | SSRI | 13 | emotion | sad>fixation | fMRI | 49 |
| Furmark19 | 2002 | social phobia | CBT | 6 | emotion | anxiogenic public speaking | PET | 14 |
| Godlewska20 | 2012 | MDD | SSRI | 42 | emotion | fear>happy | fMRI | 84 |
| Goldapple21 | 2004 | MDD | CBT | 14 | resting | resting | PET | 56 |
| Goldin22 | 2010 | SAD | mindfulness | 14 | emotion | negative self-belief>fixation | fMRI | 56 |
| Goldin23 | 2012 | SAD | CBT | 24 | emotion | negative self-referential>self | fMRI | 84 |
| Hoehn-Saric24 | 2004 | GAD | SSRI | 6 | emotion | worry>neutral | fMRI | 56 |
| Holzel25 | 2013 | GAD | mindfulness | 15 | emotion | angry>neutral | fMRI | 56 |
| Kalin26 | 1997 | MDD | SNRI | 2 | emotion | negative>neutral | fMRI | 84 |
| Keedwell27 | 2009 | MDD | variety | 12 | emotion | sad>fixation | fMRI | 28 |
| Kircher28 | 2013 | PD | CBT | 42 | emotion | fear-conditioned> non-conditioned | fMRI | 154 |
| Klumpp29 | 2013 | SAD | CBT | 14 | emotion | fearful>happy | fMRI | 42 |
| Lindauer30 | 2008 | PTSD | BEP | 10 | emotion | symptom provocation | SPECT | 56 |
| Lopez-Sola31 | 2010 | MDD | SNRI | 13 | pain | painful>nonpainful | fMRI | 56 |
| Mansson32 | 2013 | SAD | CBT (iCBT) | 13 | emotion | disgust>neutral | fMRI | 56 |
| Mansson33 | 2013 | SAD | ABM | 13 | emotion | disgust>neutral | fMRI | 84 |
| Maslowsky34 | 2010 | GAD | SSRI | 7 | emotion | angry>fixation | fMRI | 182 |
| Phan35 | 2012 | social phobia | SSRI | 21 | emotion | fear>happy | fMRI | 63 |
| Prasko36 | 2004 | PD | CBT | 6 | resting | resting | PET | 42 |
| Robertson37 | 2007 | MDD | SNRI | 10 | emotion | sad>neutral | fMRI | 182 |
| Rosenblau38 | 2012 | MDD | SSRI | 12 | emotion | negative>positive | fMRI | 56 |
| Ruhe39 | 2012 | MDD | SSRI | 16 | emotion | fear>scrambled faces | fMRI | 56 |
| Sakai40 | 2006 | PD | CBT | 11 | resting | resting | PET | 56 |
| Samson41 | 2011 | MDD | SSRI/SNRI | 10 | emotion | sad>baseline | fMRI | 84 |
| Sankar42 | 2015 | MDD | CBT | 16 | emotion | negative attitudes>neutral | fMRI | 112 |
| Schaefer43 | 2006 | MDD | SNRI | 9 | social | social interaction>other | fMRI | 63 |
| Stoy44 | 2012 | MDD | SSRI | 15 | reward | loss>neutral | fMRI | 63 |
| Tao45 | 2012 | adolescent MDD | SSRI | 19 | emotion | fear>neutral | fMRI | 84 |
| Victor46 | 2010 | MDD | SSRI | 10 | emotion | sad>neutral | fMRI | 182 |
| Wang47 | 2012 | MDD | SSRI | 18 | emotion | negative>neutral | fMRI | 112 |
| Yamanishi48 | 2009 | OCD | BT | 33 | resting | resting | SPECT | 84 |
| Yoshimura49 | 2014 | MDD | CBT | 23 | emotion | negative self-referential>verbal | fMRI | 84 |

*MDD=Major depressive disorder, GAD=generalized anxiety disorder, PD=panic disorder, PTSD=post-traumatic stress disorder, OCD=Obsessive-compulsive disorder, SAD=social anxiety disorder; fMRI=functional magnetic resonance imaging; PET=positron emission tomography; SPECT=single photon emission tomography; SSRI=selective serotonin reuptake inhibitor; SNRI=selective noradrenaline reuptake inhibitor; CBT=cognitive behavioural therapy; iCBT=internet-based CBT; CTT=cognitive trauma therapy; BT=behavioural therapy; ABM=affective bias modification; BEP=brief eclectic psychotherapy; neg=negative. Time = time from pre- to post-treatment scan reported in the paper, rounded to the nearest day.*

**Table S2. Convergence and divergence of neural changes following antidepressant medication (ADM) and psychological therapy (PT) for affective disorders.**

*Convergence of changes following ADM and PT (corrected and uncorrected results)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region | MNI coordinates | Volume (mm3) |  |  |

*x y z*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| No regions |  |  |  |  |  |  |

*Contrast: Changes following ADM minus PT (cluster-corrected)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region | MNI coordinates | Volume (mm3) | *Z* | *P* |

*x y z*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| R Med. GP/amygdala | 22 | -6 | -12 | 1704 | 3.09 | 0.001 |
| R Amygdala | 30 | -6 | -14 |  | 2.37 | 0.009 |
| R Amygdala | 25.1 | -8.3 | -20.3 |  | 2.33 | 0.01 |
| R Amygdala | 29.5 | -5.5 | -19 |  | 2.29 | 0.011 |
| R Amygdala | 28 | -6 | -26 |  | 2.26 | 0.012 |
| R Amygdala | 31.3 | -1.3 | -16.7 |  | 2.23 | 0.013 |
| R Amygdala | 26 | 2 | -24 |  | 2.12 | 0.017 |
| L Amygdala | -21 | -1 | -24 | 912 | 1.66 | 0.048 |

*Contrast: Changes following PT minus ADM (cluster-corrected)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region | MNI coordinates | Volume (mm3) | *Z* | *P* |

*x y z*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Med.  PFC | 10 | 62.7 | 16.7 | 912 | 2.33 | 0.010 |
|  | 12.3 | 57.4 | 15.1 |  | 2.20 | 0.014 |
|  | 12 | 56 | 13 |  | 2.20 | 0.014 |
|  | 10 | 60 | 22 |  | 2.14 | 0.016 |

*Convergence of changes following ADM and affect network (cluster-corrected)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region | MNI coordinates | Volume (mm3) | *ALE* |  |

*x y z*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| L Amygdala | -20 | -6 | -16 | 1848 | 0.020 |  |
| R Amygdala | 28 | -4 | -20 | 1696 | 0.024 |  |

*Convergence of changes following PT and affect network (cluster-corrected)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region | MNI coordinates | Volume (mm3) | *ALE* |  |

*x y z*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Med. PFC | 8 | 56 | 18 | 112 | 0.014 |  |

Family-wise error (FWE) cluster-corrected results for peak coordinates of each cluster. Initial ALE maps thresholded at *p*<0.05 FWE cluster-corrected (cluster-forming threshold *p*<0.001); subsequent conjunction/contrast analysis thresholded at *p*<0.05; 1000 *p*-value permutations; minimum volume for conjunction/contrast: 50mm3. MNI=Montreal Neurological Institute; L=left; R=right; Med.=medial; GP=globus pallidus; PFC=prefrontal cortex; PT=psychological therapy; ADM=antidepressant medication.

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