SUPPLEMENTAL INFORMATION

FMRI hemodynamic response function (HRF) as a novel marker of brain function: applications for understanding obsessive-compulsive disorder pathology and treatment response

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S1. Detailed information about participants

Here, we detail the inclusion/exclusion criteria for recruitment and information about medications. Those with lifetime psychotic disorders, substance dependence, bipolar disorder or ADHD were excluded, in addition to those with hoarding as a primary symptom. We allowed comorbid anxiety disorders, dysthymic disorder, depressive disorder not otherwise specified, and major depressive disorder with ADIS-IV clinical significance rating score < 6. Thirty-three participants met criteria for at least one such psychiatric comorbidity, while twelve had none. Two participants had comorbid panic disorder, 9 had generalized anxiety disorder, 17 had social anxiety disorder, 7 had major depressive disorder, 2 had dysthymia, 4 had body dysmorphic disorder, 1 had post-traumatic stress disorder, 6 had specific phobia and 1 had depressive disorder not otherwise specified. Fifteen participants took serotonin-reuptake inhibitors (6 fluoxetine, 2 escitalopram, 4 sertraline, 2 paroxetine, 1 fluvoxamine), while 29 were unmedicated. The medicated individuals did not have any changes in agent or dose for 12 weeks prior to enrollment. Fourteen unmedicated OCD individuals took psychiatric medications in the past, while sixteen were psychiatric medication-naïve. An IQ <80 on the Wechsler Abbreviated Scales of Intelligence (WASI) and medical conditions that affected cerebral metabolism like thyroid disorders, diabetes, seizures, brain tumors, a history of stroke, and multiple sclerosis were the other exclusion criteria. HCs were recruited via internet ads and flyers. They had no psychiatric disorders or substance abuse disorders and no current psychoactive medications or major medical conditions. The primary clinical measure for OCD was the Yale-Brown Obsessive-Compulsive Scale (YBOCS) [1]. We obtained secondary measures, viz. Montgomery-Åsberg Depression Rating Scale (MADRS) [2] and Hamilton Anxiety Scale (HAMA) [3]. Social and occupational performance and general functionality were rated using the Global Assessment Scale (GAS) [4].

S2. Relationship of the HRF to normal brain function

To test the relationship of the HRF to normal brain function, we performed a pilot proof of concept analysis using handedness, with the hypothesis that the HRF is sensitive to normal brain function. This index, the Edinburgh Handedness Scale [5], was acquired for assessment and screening purposes in our HC sample and reflects longstanding patterns of motor behavior.

Similar to prior studies [6], we determined the relationship between the HRF shape in hand-movement-related primary motor cortex (MC) regions and handedness. It must be noted that we probed this post-hoc, and the study was not initially designed for this; hence, our findings must only be considered as preliminary, and for kindling further research on this topic.

We tested the sensitivity of the HRF to normal brain function with simple testing involving motor function in HC. We identified bilateral centroids in the MC using Neurosynth (*www.neurosynth.org*), with the meta-analysis search term "handedness" (centroids in MNI space- left MC: -36,-24,58, right MC: 36,-24,58). Instead of using conventional anatomical ROIs, Neurosynth was chosen to derive functionally defined ROIs relevant for addressing handedness. We defined the regions-of-interest (ROIs) as spheres of radius 5mm around the centroids, masked by a 50% gray matter mask. Average fMRI time series were obtained from these ROIs, and deconvolution was performed to derive the HRF parameters. The difference in HRF parameters was obtained between the right and left MC ROIs, and the association between them and percentage right handedness from the Edinburgh Handedness Scale [5] was obtained through linear regression separately for each HRF parameter.

In HC we found a significant association between the difference in HRF RH between right and left MC (i.e. HRF RH in right -minus- left MC regions) and percentage right handedness ($R=-0.57$, $R^2=0.33$, $P= 0.0028$) (**Fig.S1**). The direction of this association was expected, since the Edinburgh Handedness score is an index that is a relative measure of right- vs. left-handedness. Higher HRF RH in left compared to right MC was associated with higher right-handedness. Ten out of 13 persons with 100% right handedness exhibited higher HRF RH in the left MC compared to the right MC. Among those with less than 100% right-handedness, 8 out of 12 persons had higher HRF RH in the right MC compared to the left MC.

We also assessed various quality measures of regression (see section S8) to find that the regression did not violate the homoscedasticity assumption ($P=0.90$, Engle's ARCH test), and no influential observations were found ($P<0.018$, leave-one-out regressions), although the residuals were not uniformly distributed ($P=8\times10^{-5}$, Chi-square goodness-of-fit test) perhaps due to having some saturated handedness values.

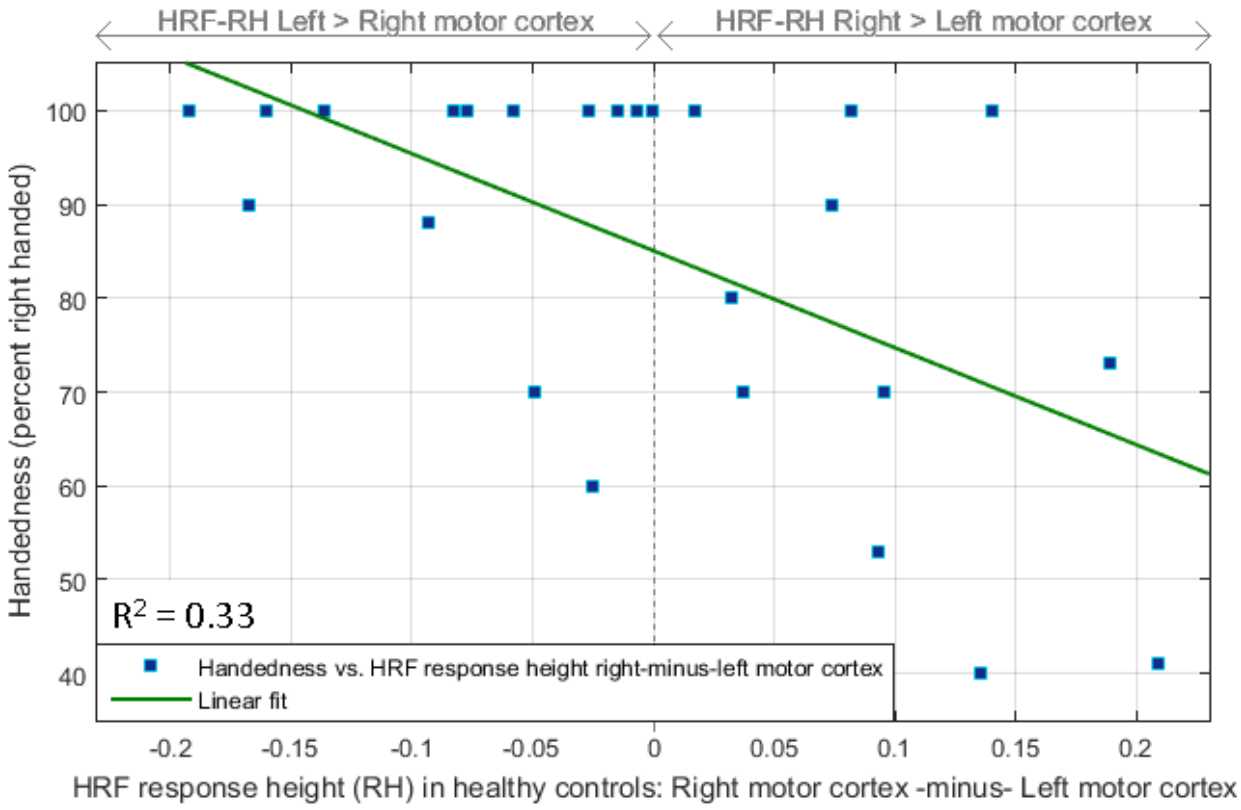

Fig. S1. *Association between the difference in response height (RH) of the hemodynamic response function (HRF) between right and left primary motor cortices [MC] (i.e. RH in right -minus- left MC regions) and percentage right handedness. Higher RH in left compared to right MC was associated with higher right-handedness. 10 out of 13 persons with 100% right handedness had higher RH in the left MC compared to the right MC. Among those with less than 100% right handedness, 8 out of 12 persons had higher RH in the right MC compared to the left MC. R=–0.5715, R^2=0.3266, P= 0.0028.*

These findings serve as a preliminary proof-of-concept as it was demonstrated on data available to us at the time. By no means was this an exhaustive test, but provided a preliminary assessment of the sensitivity of HRF to normal brain function. The study sample was comprised of all right handers per our inclusion/exclusion criteria, with about half being 100% right handed; hence, our observations could be saturated to some extent. Given that this was a pilot test, future studies focusing primarily on the healthy brain, are needed to examine possible relationships of the HRF shape with other aspects of normal brain functioning.

S3. Longitudinal reliability of the HRF

We assessed test-retest reliability of HRF by quantifying the intra-class correlation (ICC) between HRF parameters from scans spaced 4 weeks apart. One of the reasons for us to propose the use of the HRF as a marker of brain function and pathology was that the HRF is considered to be relatively stable over time [7] [8]. Two sessions of fMRI data were available to us, spaced 4 weeks apart, for two cases: (i) healthy controls, (ii) a subset of the OCD group (N=21, OCD-subset group), who had also been scanned 4 weeks prior to the beginning of treatment in addition to the pre- and post-CBT scans. We tested the test-retest consistency of the HRF over 4 weeks in HCs and the OCD-subset group (4 weeks prior versus onset of treatment) separately by computing ICC of HRF RH across the two sessions. We employed the *Cronbach's alpha* ICC measure (random effects, multiple measurements) [9]. The ICC ranges from -1 to 1, with a higher absolute value implying higher stability.

We found significant brain-wide intra-class correlation between successive scans in HCs ($r=0.5117$, $p<0.00001$) and in the OCD-subset group ($r=0.5063$, $p<0.00001$). These values reflect moderate reliability [9]. This provides evidence of moderate stability over time in both healthy and pathological populations. It must be noted that the two scans were spaced 4 weeks apart, which is long enough for non-pathological routine changes to take place in brain structure and chemistry, which might have resulted in some HRF change over these 4 weeks at the individual-participant level (although no statistically significant changes at the group level were observed, as revealed by our analysis presented in main text). Hence, we posit that the test-retest reliability of the HRF (i.e. the ICC) would be higher when assessed for scans spaced hours or few days apart (open to investigation). These factors could be taken under consideration in future studies to assess the suitability of HRF as a marker of brain function and pathology. Aguirre et. al. [8] assessed temporal stability of HRF, but only in the central sulcus and only in 4 healthy participants, while the current study assessed it at the whole-brain level in a larger cohort.

S4. fALFF analysis

To compare the HRF against another regional resting-state fMRI measure that is known to be sensitive to pathology, we examined the similarities and differences between HRF findings and results from a similar analysis using fractional amplitude of low frequency fluctuations (fALFF).

Specifically, we compared HRF group difference maps with the group difference maps of fALFF. FALFF is a regional measure derived from voxel-level fMRI data, which is widely understood and utilized to study brain function [10]. It measures the strength of low frequency (0.01-0.1 Hz) fMRI fluctuations, i.e. a measure of resting-state BOLD amplitude. On the other hand, HRF RH measures HRF amplitude. Since BOLD power is primarily concentrated in this low frequency range, it is not unreasonable to hypothesize that fALFF and RH must both be related to the amplitude of neural activity as well as with each other.

To test this, we computed the voxel-level fALFF Z-score [11], and identified significant fALFF differences between Session-1 HC and pre-CBT OCD (statistical methods and thresholds identical to HRF analysis). We masked the statistical map with only those regions found to have significant differences in RH, TTP and FWHM between Session-1 HC and pre-CBT OCD. We did masking because the focus of this study was the HRF, and we performed fALFF analysis only to compare with the HRF findings. We then measured the percentage of significant fALFF voxels that overlapped (intersection) with the RH group difference map. We did the same for TTP and FWHM. We predicted that the fALFF map would exhibit largest similarity with the RH map compared to the TTP and FWHM maps.

We found that the fALFF map had 80.95% overlap with the RH map, 16.67% overlap with the TTP map and 7.94% with the FWHM map (note: percentages do not sum to 100 since the RH, TTP and FWHM maps themselves had a tiny fraction of common voxels.) Despite significant overlap between the RH and fALFF maps, there were no significant associations between the two in any of the common voxels, suggesting that HRF RH is distinct from fALFF, despite sharing certain biophysical bases.

As predicted, the fALFF map had highest similarity with the RH map (80.95% overlap), likely reflecting common biophysical phenomena underlying these measures. However, RH and fALFF were not statistically associated in any of the common voxels, suggesting distinction amid seemingly apparent similarities. It remains to be understood what exact relationship these two measures share, although conceptually RH is an absolute measurement while fALFF is by definition fractional and thus dependent on the amplitude of activations in other frequency bands. Low similarity with the TTP and FWHM maps also underscores that these two are distinct from measures related to the amplitude of brain activity such as fALFF and RH. In summary, these findings lend credence to our prediction that fALFF would be more similar to RH than TTP or

FWHM, yet nevertheless show important distinction from RH. These findings help us further understand the understudied HRF from the perspective of a widely-used regional measure derived from resting-state fMRI, the fALFF.

Additionally, we performed machine learning prediction analysis for comparison using fALFF features, using the procedure identical to the one applied to HRF features (presented in main text). We used voxels that exhibited significant fALFF difference for pre-CBT OCD vs Session-1 HC comparison (similar to hypothesis-1), and observed an accuracy of 72.39% (significantly greater than chance, $P<10^{-30}$). This accuracy was significantly lower than the accuracy of 86.4% obtained using HRF ($P<10^{-30}$).

S5. ANOVA results

Here we present the 2-way ANOVA results performed prior to the pairwise T-tests. We performed a 2-way ANOVA with group and time as factors (HC vs OCD and session-1 vs session-2), separately for each HRF parameter ($p<0.05$, cluster-level and FDR thresholded, controlled for age, education and head-motion). We found a significant main effect of group (**Fig.S2a-c**) and a significant main effect of time (**Fig.S2d-f**) with all 3 HRF parameters, and a significant group×time interaction with RH and TTP (**Fig.S3**).

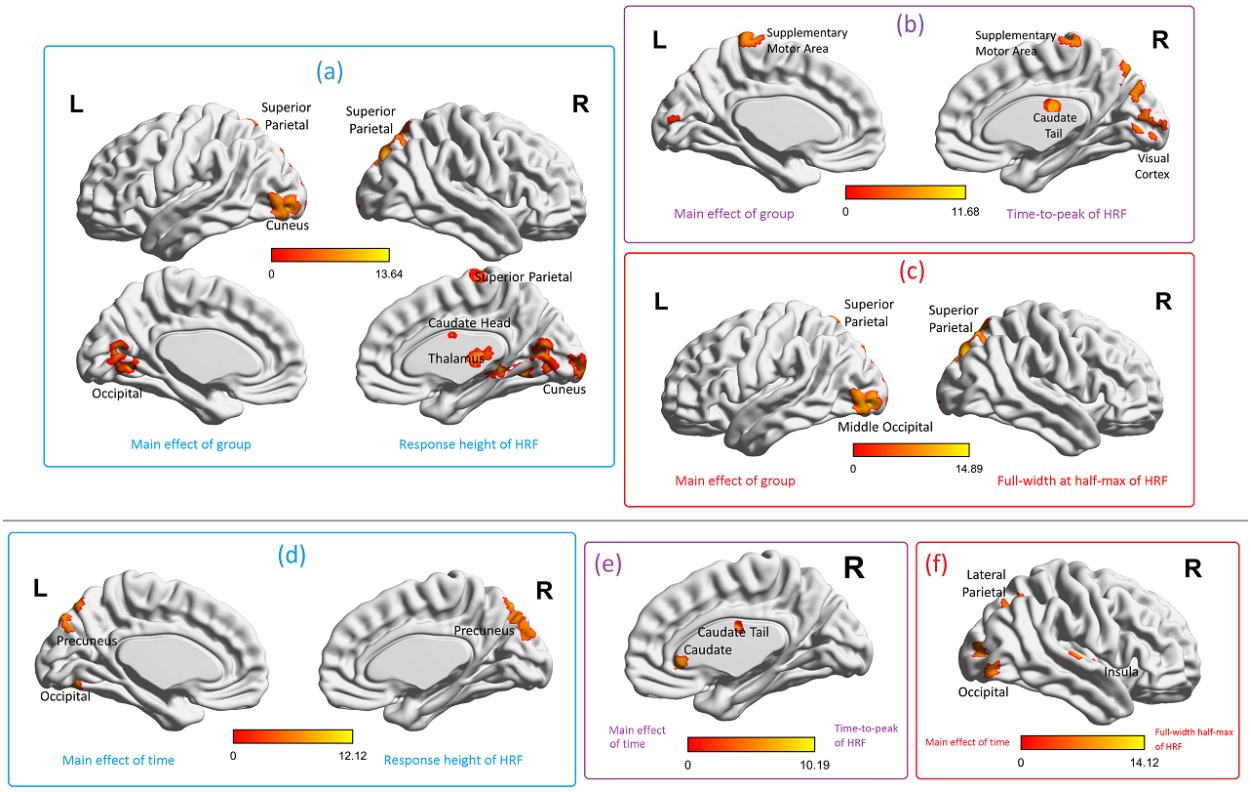

Fig. S2. *Hemodynamic response function (HRF) findings with the 2-way ANOVA: significant main effect of group (HC vs OCD) (a-c), and significant main effect of time (session-1 vs session-2) (d-f).* ***(a)*** *Effect of group with response height (RH) of the HRF.* ***(b)*** *Effect of group with time-to-peak (TTP) of the HRF.* ***(c)*** *Effect of group with full-width at half-max (FWHM) of the HRF.* ***(d)*** *Effect of time with response height (RH) of the HRF.* ***(e)*** *Effect of time with time-to-peak (TTP) of the HRF.* ***(f)*** *Effect of time with full-width at half-max (FWHM) of the HRF. The color bars correspond to the F-values.*

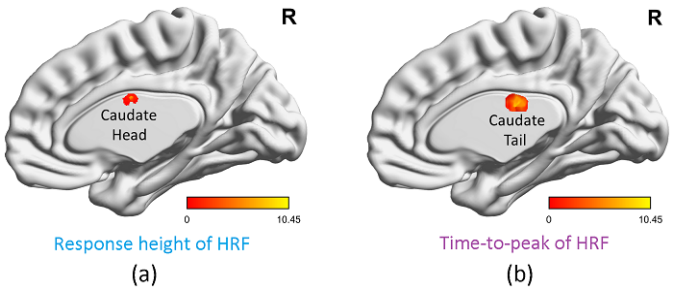

Fig. S3. *Hemodynamic response function (HRF) findings with the 2-way ANOVA: significant group×time interaction effect with* ***(a)*** *response height (RH) of the HRF, and* ***(b)*** *time-to-peak (TTP) of the HRF. The color bars correspond to the F-values.*

S6. Effect of medication

Our OCD group consisted of 15 medicated and 29 unmedicated participants, as described in section S1. To assess the effect of medication status on the HRF in this group, we performed two analyses, viz. (i) medicated vs. unmedicated participants, and (ii) entire OCD sample (N=44) vs. unmedicated participants (N=29). The former comparison was to assess if medicated participants' HRFs differed from unmedicated participants, while the latter comparison was to assess how participants with no medications compared with the entire OCD sample used in this study. These analyses were performed separately with both session-1 and session-2 data. Since our interest was to assess the impact of medication on our HRF findings, and not to identify any whole-brain HRF map of the effect of medication, we restricted (masked) the analysis to only those regions that emerged significant in our main HRF analysis. We obtained voxel-level maps for each of these 12 comparisons, with each voxel having a specific T-value and P-value for the corresponding comparison. Here we summarize our findings by reporting the highest T-value and lowest P-value among all the tested voxels for each comparison.

Results showed no significant differences in either of the two tested cases. Specifically, medicated and unmedicated participants showed no significant differences at baseline in RH ($T<1.16$, $P>0.25$), TTP ($T<1.09$, $P>0.28$) and FWHM ($T<0.94$, $P>0.35$), and after CBT in RH ($T<1.21$, $P>0.23$), TTP ($T<0.99$, $P>0.33$) and FWHM ($T<1.12$, $P>0.27$). Likewise, the entire OCD sample and unmedicated participants showed no significant differences at baseline in RH ($T<1.02$, $P>0.31$), TTP ($T<1.20$, $P>0.23$) and FWHM ($T<1.19$, $P>0.24$), and after CBT in RH

(T<0.96, P>0.34), TTP (T<0.89, P>0.38) and FWHM (T<1.14, P>0.26). These observations highlight the negligible impact of medication on our HRF findings.

S7. Effect of depressive symptoms

Seven OCD participants had major depressive disorder and 1 had depressive disorder not otherwise specified. Among these 8 participants, 6 participants showed reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) [2] from session-1 to session-2 by 52.2±11.1%, while 2 participants showed increase by 16.7±3.9%. Baseline MADRS values were not significantly associated with HRF parameters at baseline in the regions showing significant group differences among these 8 participants (P>0.12, median(P)=0.44) nor across the entire sample (P>0.17, median(P)=0.75). Likewise, change in MADRS values across sessions were not significantly associated with change in HRF parameters across sessions in the regions showing significant differences across sessions among these 8 participants (P>0.28, median(P)=0.74) nor across the entire sample (P>0.53, median(P)=0.71). From these observations, we can deduce that depressive symptoms did not affect our results either at baseline or across sessions in either the entire sample or among those with comorbid depressive symptoms.

S8. Assessing the quality of regression fits

In this study, we assessed two associations using linear regression: (i) the association between percentage change in HRF RH and percentage change in OCD severity with treatment, and (ii) the association between pre-CBT HRF RH and post-treatment OCD severity. Here we present certain quality assurance analyses of the regression fits.

We found significant negative association between (Fig.5a in main text) percentage change in HRF RH and percentage change in OCD severity (YBOCS) with CBT treatment (R=–0.44, R^2=0.19, P=0.0028) in the caudate head region. We plotted the residuals against each variable (**Fig.S4**). We performed the Engle's ARCH test for residual heteroscedasticity to find that the homoscedasticity assumption was not violated (P=0.20).

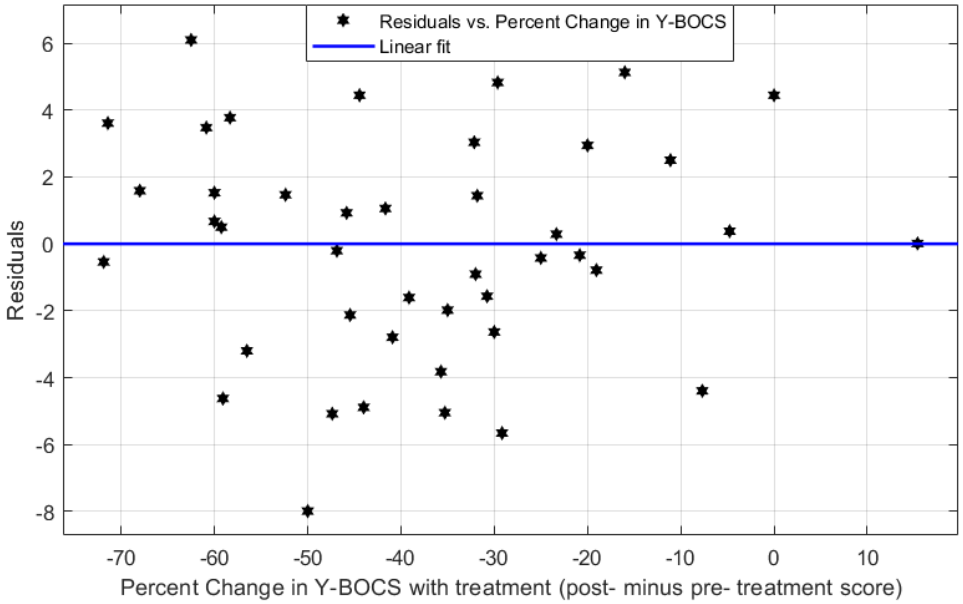

Fig. S4. *Plot of the residuals against percentage change in OCD severity with treatment. The residuals were determined as the difference between the percentage change in HRF RH values and the regression fit as in Fig.5a in the main text.*

We also assessed the distribution of residuals to find that the residuals were uniformly distributed (P=0.73, Chi-square goodness-of-fit test), and were not Gaussian distributed ($P=10^{-3}$, one-sample Kolmogorov-Smirnov test). We also tested for the presence of influential observations by performing leave-one-out regression, i.e. we iteratively repeated the regression by discarding exactly one participant (data point) in each iteration (thus performing 44 iterations for 44 OCD participants), and assessing if discarding any of the participants resulted in non-significant associations. If such non-significant associations were to arise then the corresponding left out data points would be labeled as influential observations. We found no influential observations (R=-0.49 to -0.40; R^2=0.16 to 0.24; P=0.0009 to 0.008).

Next, we found a significant negative association between pre-CBT HRF RH in the caudate head and OCD severity (YBOCS) after treatment (R=–0.48, R^2=0.23, P= 0.001) (Fig.5b in main text). We plotted the residuals against each variable (**Fig.S5**). We performed the Engle's ARCH test for residual heteroscedasticity to find that the homoscedasticity assumption was not violated (P=0.76).

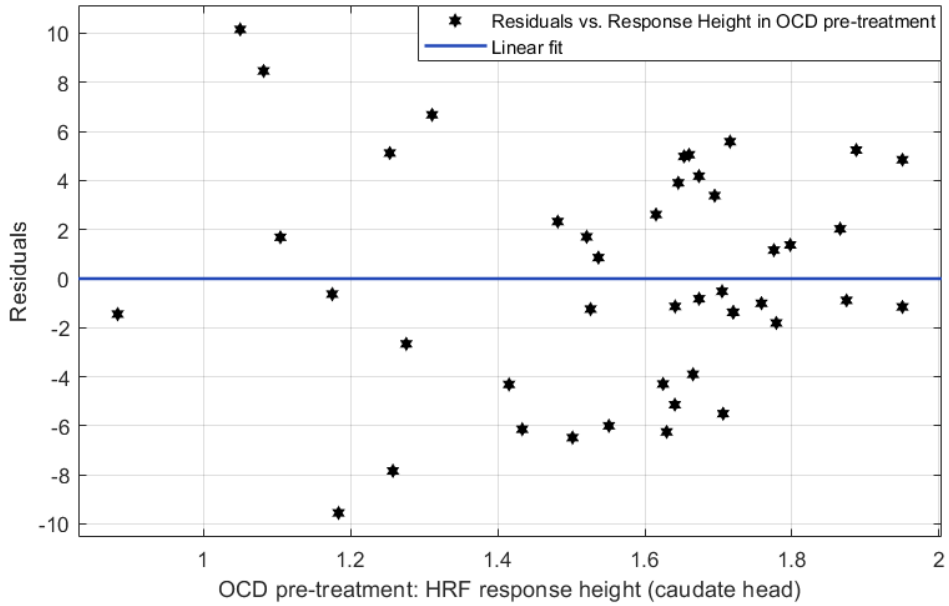

Fig. S5. *Plot of the residuals against pre-treatment HRF RH in OCD. The residuals were determined as the difference between post-treatment OCD severity values and the regression fit as in Fig.5b in the main text.*

We also assessed the distribution of residuals to find that the residuals were uniformly distributed (P=0.14, Chi-square goodness-of-fit test), and were not Gaussian distributed ($P=4\times10^{-5}$, one-sample Kolmogorov-Smirnov test). We also tested for the presence of influential observations by performing leave-one-out regression, as before. We found no influential observations (R=-0.54 to -0.40; R^2=0.16 to 0.29; P=0.0002 to 0.0076).

S9. Relationship among the HRF parameters

Although it is intuitive to associate lower RH with larger TTP or FWHM, it may not always be the case. For example, a recent study found lower RH in aging and in those with vascular risk but no altered TTP or FWHM in those cases [12]. Likewise, in our study the majority of regions showing RH changes were not associated with TTP or FWHM changes. Within our data, we did not observe significant correlation across subjects between whole-brain HRF parameters. Specifically, in healthy controls, RH and TTP were not significantly correlated (mean R=0.176, median P=0.09), nor were RH and FWHM (mean R=0.054, median P=0.46) or TTP and FWHM

(mean R=0.145, median P=0.51). In OCD, RH and TTP were not significantly correlated (mean R=0.225, median P=0.06), nor were RH and FWHM (mean R=0.055, median P=0.42) or TTP and FWHM (mean R=0.136, median P=0.26). RH and TTP seem to be slightly more related than RH and FWHM, and even slightly more than TTP and FWHM. Despite these observations, based on the underlying biophysics, there is sufficient grounds to hypothesize a direct relationship between the HRF parameters in healthy adults, as well as a shift in that relationship in brain-related illnesses. Thoroughly addressing these questions is beyond the scope of this study, however. Further research is necessary to address these important questions.

S10. Discussion on HRF estimation using resting-state fMRI data

In this study, we estimated the HRF using resting-state fMRI data using a data-driven approach proposed by Wu et al. [13]. An alternative to estimating HRF from resting-state fMRI data would be to estimate it from event-related task fMRI data. A major drawback with such an approach is that any specific event-related task does not activate the entire brain uniformly [14]; different brain regions respond differently to the task events. Also, different tasks elicit different patterns of response. Some regions may show the expected pattern of immediate BOLD signal increase after an event, while some other regions may show BOLD signal decrease, or even a signal decrease in the beginning followed by an increase later. For example, the study by Gonzalez-Castillo et al. found a prolonged dip in the hemodynamic response in certain prefrontal regions during a simple event-related visual task, which is completely uncharacteristic of the canonical HRF shape [7] [8]. Despite these challenges, another recent study tried to estimate the HRF from event-related task fMRI data [15] and found that even a simple task that was expected to activate the majority of the brain was able to activate only 77% of the gray matter voxels; additionally, similar observations of negative hemodynamic responses as well as hemodynamic responses of strange shapes were observed in activated voxels. In this context, it is important to recognize that the HRF is different from a “hemodynamic response”; the HRF is a transfer function linking neural activity to local blood flow, while a “hemodynamic response” is the measured fMRI response to a task.

It thus appears problematic to use event-related task fMRI to estimate the HRF for the purpose of understanding brain function (or pathology and treatment response) for two reasons:

(i) whole-brain HRF cannot be estimated in every voxel using the events from the task because any given task is unlikely to activate the whole brain. (ii) Even among activated voxels, the hemodynamic response to the task events may be non-uniform. The definition of the HRF is violated if negative or strange shape HRFs are estimated – the HRF is the hemodynamic response in the local blood vessel to a unit neural event in the nearby neurons, which has been shown to always have a shape similar to a double-gamma function [16] [17]. For example, a negative hemodynamic response may be observed due to a dip in neural activity during a task, yet the HRF is still positive (note the distinction between the measured hemodynamic response and the HRF here). Consistent with invasive electrophysiological evidence [18], the HRF typically has an initial ascent following the event, a maximum response (response height) that occurs sometime after the event (time-to-peak), a descent, a post-stimulus undershoot and a return to baseline (refer to Fig.2 in main text). For these reasons, extremely few studies have attempted to study HRFs estimated from event-related task fMRI data, and a majority of the literature on HRF is based on those estimated from resting-state fMRI data. HRF estimation using resting-state fMRI data using Wu et al's technique [13] does not face these shortcomings because the pseudoevents are identified in a data-driven fashion using large BOLD events in the time series that resemble the characteristic HRF shape; and, since the pseudoevents are not based on any specific task, we can estimate HRF across the whole brain. These are among the factors that motivated us to estimate whole-brain HRF in this study using resting-state fMRI data, as in previous studies [19] [13] [20] [21] [22] [23] [24] [25].

SUPPLEMENTAL REFERENCES

[1] W. Goodman, L. Price, S. Rasmussen, C. Mazure, R. Fleischmann, C. Hill, G. Heninger and D. Charney, "The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability," *Archives of General Psychiatry,* vol. 46, no. 11, pp. 1006-11, 1989.

[2] S. Montgomery and M. Asberg, "A new depression scale designed to be sensitive to change," *The British Journal of Psychiatry,* vol. 134, pp. 382-389, 1979.

[3] M. Hamilton, "The assessment of anxiety states by rating," *The British Journal of*

Psychiatry, vol. 32, no. 1, pp. 50-55, 1959.

[4] J. Endicott, R. Spitzer, J. Fleiss and J. Cohen, "The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance," *Archives of General Psychiatry,* vol. 33, no. 6, pp. 766-771, 1976.

[5] R. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," *Neuropsychologia,* vol. 9, no. 1, pp. 97-113, 1971.

[6] E. Pool, A. Rehme, G. Fink, S. Eickhoff and C. Grefkes, "Handedness and effective connectivity of the motor system," *Neuroimage,* vol. 99, pp. 451-60, 2014.

[7] D. A. Handwerker, J. M. Ollinger and M. D'Esposito, "Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses," *Neuroimage,* vol. 21, no. 4, pp. 1639-51, 2004.

[8] G. K. Aguirre, E. Zarahn and M. D'esposito, "The variability of human, BOLD hemodynamic responses," *Neuroimage,* vol. 8, no. 4, pp. 360-9, 1998.

[9] T. Koo and M. Li, "A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research," *J Chiropr Med.,* vol. 15, no. 2, pp. 155-63, 2016.

[10] R. Tadayonnejad, S. Yang, A. Kumar and O. Ajilore, "Clinical, cognitive, and functional connectivity correlations of resting-state intrinsic brain activity alterations in unmedicated depression," *Journal of Affective Disorders,* vol. 172, pp. 241-50, 2015.

[11] X. Zuo, A. Di Martino, C. Kelly, Z. Shehzad, D. Gee, D. Klein, F. Castellanos, B. Biswal and M. Milham, "The oscillating brain: complex and reliable," *Neuroimage,* vol. 49, no. 2, pp. 1432-45, 2010.

[12] I. McDonough, A. Bender, L. Patihis, E. Stinson, S. Letang and W. Miller, "The Trouble Interpreting fMRI Studies in Populations with Cerebrovascular Risk: The Use of a Subject-Specific Hemodynamic Response Function in a Study of Age, Vascular Risk, and Memory," *bioRxiv,* p. 512343, 2019.

[13] G. Wu, W. Liao, S. Stramaglia, J. Ding, H. Chen and D. Marinazzo, "A blind deconvolution approach to recover effective connectivity brain networks from resting state fMRI data," *Medical Image Analysis,* vol. 17, no. 3, pp. 365-374, 2013.

[14] J. Gonzalez-Castillo, Z. Saad, D. Handwerker, S. Inati, N. Brenowitz and P. Bandettini,

"Whole-brain, time-locked activation with simple tasks revealed using massive averaging and model-free analysis," *Proc Natl Acad Sci USA,* vol. 109, no. 14, pp. 5487-92, 2012.

[15] A. Taylor, J. Kim and D. Ress, "Characterization of the hemodynamic response function across the majority of human cerebral cortex," *Neuroimage,* vol. 173, pp. 322-331, 2018.

[16] R. Buxton, "Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques," *Energy,* vol. 24, no. 2, pp. xi, 523, 2002.

[17] R. Buxton, E. Wong and L. Frank, "Dynamics of blood flow and oxygenation changes during brain activation: the balloon model," *Magnetic Resonance in Medicine,* vol. 39, no. 6, pp. 855-64, 1998.

[18] N. Logothetis, J. Pauls, M. Augath, T. Trinath and A. Oeltermann, "Neurophysiological investigation of the basis of the fMRI signal," *Nature,* vol. 412, pp. 150-157, 2001.

[19] D. Rangaprakash, G.-R. Wu, D. Marinazzo, X. Hu and G. Deshpande, "Hemodynamic response function (HRF) variability confounds resting-state fMRI functional connectivity," *Magnetic Resonance in Medicine,* p. in press, 2018.

[20] D. Rangaprakash, M. N. Dretsch, W. Yan, J. S. Katz, T. S. Denney and G. Deshpande, "Hemodynamic variability in soldiers with trauma: Implications for functional MRI connectivity studies," *NeuroImage: Clinical,* p. in press, 2017.

[21] M. Boly, S. Sasai, O. Gosseries, M. Oizumi, A. Casali, M. Massimini and G. Tononi, "Stimulus set meaningfulness and neurophysiological differentiation: a functional magnetic resonance imaging study," *PLoS One,* vol. 10, no. 5, p. e0125337, 2015.

[22] E. Amico, F. Gomez, C. Di Perri, A. Vanhaudenhuyse, D. Lesenfants, P. Boveroux, V. Bonhomme, J. F. Brichant, D. Marinazzo and S. Laureys, "Posterior cingulate cortex-related co-activation patterns: a resting state FMRI study in propofol-induced loss of consciousness," *PLoS One,* vol. 9, no. 6, p. e100012, 2014.

[23] D. Rangaprakash, M. N. Dretsch, W. Yan, J. S. Katz, T. S. Denney and G. Deshpande, "Hemodynamic response function parameters obtained from resting-state functional MRI data in soldiers with trauma," *Data in Brief,* vol. 14, pp. 558-562, 2017.

[24] D. Rangaprakash, G. Deshpande, T. Daniel, A. Goodman, J. Robinson, N. Salibi, J. Katz, T. Denney and M. Dretsch, "Compromised Hippocampus-Striatum Pathway as a Potential

Imaging Biomarker of Mild Traumatic Brain Injury and Posttraumatic Stress Disorder," *Human Brain Mapping,* vol. 38, no. 6, pp. 2843-2864, 2017.

[25] B. Lamichhane, B. M. Adhikari, S. F. Brosnan and M. Dhamala, "The neural basis of perceived unfairness in economic exchanges," *Brain Connectivity,* vol. 4, no. 8, pp. 619-30, 2014.