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The salience network causally influences default mode network activity during moral reasoning

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Large-scale brain networks are integral to the coordination of human behaviour, and their anatomy provides insights into the clinical presentation and progression of neurodegenerative illnesses such as Alzheimer's disease, which targets the default mode network, and behavioural variant frontotemporal dementia, which targets a more anterior salience network. Although the default mode network is recruited when healthy subjects deliberate about 'personal' moral dilemmas, patients with Alzheimer's disease give normal responses to these dilemmas whereas patients with behavioural variant frontotemporal dementia give abnormal responses to these dilemmas. We hypothesized that this apparent discrepancy between activation- and patient-based studies of moral reasoning might reflect a modulatory role for the salience network in regulating default mode network activation. Using functional magnetic resonance imaging to characterize network activity of patients with behavioural variant frontotemporal dementia and healthy control subjects, we present four converging lines of evidence supporting a causal influence from the salience network to the default mode network during moral reasoning. First, as previously reported, the default mode network is recruited when healthy subjects deliberate about 'personal' moral dilemmas, but patients with behavioural variant frontotemporal dementia producing atrophy in the salience network give abnormally utilitarian responses to these dilemmas. Second, patients with behavioural variant frontotemporal dementia have reduced recruitment of the default mode network compared with healthy control subjects when deliberating about these dilemmas. Third, a Granger causality analysis of functional neuroimaging data from healthy control subjects demonstrates directed functional connectivity from nodes of the salience network to nodes of the default mode network during moral reasoning. Fourth, this Granger causal influence is diminished in patients with behavioural variant frontotemporal dementia. These findings are consistent with a broader model in which the salience network modulates the activity of other large-scale networks, and suggest a revision to a previously proposed 'dual-process' account of moral reasoning. These findings also characterize network interactions underlying abnormal moral reasoning in frontotemporal dementia, which may serve as a model for the aberrant judgement and interpersonal behaviour observed in this disease and in other disorders of social function. More broadly, these findings link recent work on the dynamic interrelationships between large-scale brain networks to observable impairments in dementia syndromes, which may shed light on how diseases that target one network also alter the function of interrelated networks.

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Abbreviation: FTD = frontotemporal dementia

Introduction

The task-related functions and interrelationships of large-scale intrinsic functional brain networks are matters of controversy and ongoing investigation. A salience network anchored by the anterior insula and anterior cingulate has been hypothesized to play a central regulatory role in organizing neural responses to homeostatically significant stimuli (Dosenbach *et al.*, 2006; Seeley *et al.*, 2007; Sadaghiani *et al.*, 2010). The salience network is often activated by attention-demanding cognitive tasks, as is an executive control network including dorsal frontoparietal cortex. These networks are reciprocally related to a default mode network including the precuneus/posterior cingulate cortex, lateral parietal cortex and medial prefrontal cortex (Raichle *et al.*, 2001; Fox *et al.*, 2005). While the default mode network is deactivated by many attention-demanding tasks, it is recruited for some cognitive operations such as autobiographical memory, prospection, theory of mind, navigation, and 'personal' moral reasoning (Greene *et al.*, 2001; Harrison *et al.*, 2008; Spreng *et al.*, 2009). Consistent with a regulatory role for the salience network, recent studies provide evidence for causal influences from the salience network in modulating the activity of the default mode network and executive control network (Rilling *et al.*, 2008; Sridharan *et al.*, 2008; Bonnelle *et al.*, 2012).

These large-scale brain networks also influence the presentation and progression of neurodegenerative illnesses like Alzheimer's disease and behavioural variant frontotemporal dementia (FTD), in which the characteristic clinical courses of disease reflect the spread of pathology within targeted networks. For example, while Alzheimer's disease causes atrophy and decreased connectivity within the default mode network (Greicius *et al.*, 2004; Seeley *et al.*, 2009), behavioural variant FTD targets the salience network (Seeley *et al.*, 2009; Zhou *et al.*, 2010). Given these targeted effects, the clinical syndromes associated with these illnesses may elucidate the behavioural consequences of disruption within different networks; furthermore, understanding the interactions between large-scale networks may provide insights into the clinical progression and cognitive effects of neurodegenerative disease.

There is an apparent discrepancy, however, between results from activation-based and patient-based methods regarding the role of the default mode network in moral reasoning. In functional MRI studies of healthy subjects, nodes of the default mode network are activated during hypothetical reasoning about 'personal' moral dilemmas—e.g. dilemmas in which the best overall outcome can only be produced by violating someone's personal rights (Greene *et al.*, 2001, 2004; Harrison *et al.*, 2008). This finding might suggest that default mode network dysfunction in Alzheimer's disease should cause abnormal judgements in these dilemmas; instead, behavioural studies in patients demonstrate relatively normal personal moral judgement in Alzheimer's disease, whereas patients with behavioural variant FTD are more likely than healthy control subjects to endorse violating someone's personal rights (Mendez and Shapira, 2009). A similar pattern has been observed in patients with structural lesions to prefrontal cortex including both the medial prefrontal node of the default mode network and the anterior cingulate node of the salience network (Ciaramelli *et al.*, 2007; Koenigs *et al.*, 2007).

We aimed to reconcile the findings of activation-based and patient-based studies of the default mode network in personal moral reasoning by using functional MRI to study neural activity in patients with behavioural variant FTD and in normal control subjects during a moral reasoning task. Based on the proposed role of the salience network in regulating the activity of other brain networks, we hypothesized that the salience network plays a causal role in recruiting the default mode network during 'personal' moral dilemmas, and that abnormal moral judgement in behavioural variant FTD reflects a disruption of this causal influence. We compared univariate differences in default mode network recruitment during deliberation about personal moral dilemmas between patients with behavioural variant FTD and control subjects, and used Granger causality analysis to characterize the dynamics and directionality of network activity in patients with behavioural variant FTD and control subjects.

Materials and methods

Patients and control subjects

Eleven patients were diagnosed with behavioural variant FTD based on International Behavioral Variant FTD Criteria Consortium criteria (Rascovsky *et al.*, 2011) by a multidisciplinary team of neurologists, neuropsychologists and nurses after a comprehensive evaluation including a clinical history, neurological examination and extensive neuropsychological testing. Patients were recruited in early stages of illness because of the cognitive demands of the moral reasoning task. Of the 11 patients, one was excluded from behavioural and neuroimaging analyses for inability to perform the task (with repeated random responses prior to the complete presentation of the question prompt), and two more patients were included in behavioural analyses but excluded from neuroimaging analyses because of excessive head motion. Sixteen healthy older control subjects were verified as normal on the basis of a neurological examination, neuropsychological testing and structural MRI. Demographic, clinical and neuropsychological data for the 10 patients and 16 control subjects included in the behavioural analysis are summarized in Table 1. There was a trend towards older age in the control subjects, and a greater proportion of control subjects were female.

All participants gave written informed consent according to the Declaration of Helsinki, and the study was approved by the Committee on Human Research at UCSF.

Moral reasoning task

We modified a moral reasoning task that has been previously described (Greene *et al.*, 2001, 2004) to address criticisms of the

Table 1 Demographic, clinical and neuropsychological characteristics of patients and control subjects

Characteristics	Behavioural variant FTD ($n = 10$)	Control subjects ($n = 16$)
Demographic		
Age (years)	61.2 (6.5)	66.0 (5.5)
M/F	6/4*	6/10
Education (years)	16.6 (2.3)	17.7 (1.8)
Clinical		
MMSE (30)	28.3 (1.4)*	29.5 (0.6)
CDR total	1.1 (0.6)*	0
CDR sum of boxes	6.1 (3.4)*	0.0 (0.1)
Executive		
Digits forward	6.5 (1.4)	7.3 (1.1)
Digits backward	4.4 (1.4)*	5.5 (1.1)
Modified Trails (lines per minute)	19.2 (15.6)*	35.8 (16.2)
Stroop naming	64.1 (14.3)*	96.7 (12.1)
Stroop interference	35.8 (16.7)*	55.1 (8.3)
Calculations (5)	4.6 (0.7)	4.7 (0.5)
Language		
Boston naming test (15)	11.9 (2.5)*	14.3 (0.7)
Repetition (5)	4.3 (0.8)*	4.9 (0.3)
Auditory word recognition (PPVT, 16)	13.9 (2.3)*	15.8 (0.4)

Values represent mean (SD).
*Characteristics on which patients significantly differ from control subjects ($P < 0.05$, t-tests with unequal variance).
CDR = Clinical Dementia Severity Rating Scale; MMSE = Mini-Mental Status Examination; PPVT = Peabody Picture Vocabulary Test.

original task and to tailor the task for use in patients with dementia. These modifications are detailed in the online Supplementary material. Participants made judgements about 21 hypothetical dilemmas presented as synchronized text and audible narration through a series of three screens. The first two screens presented a vignette describing the dilemma, and the third posed a question about whether the subject would perform a hypothetical action in response to the situation ('Would you . . . in order to . . . ?'). The two vignette screens were presented over 34 s, and the question was presented over 5.5 s with an additional 6.5 s allowed for response time. Each dilemma was followed by an intertrial interval of 14 s; therefore, total presentation time for each dilemma was 1 min. Dilemmas were divided among three conditions: non-moral practical dilemmas; moral dilemmas involving an impersonal weighting of harms and benefits; and moral dilemmas involving utilitarian infringements of personal rights. Dilemmas were reviewed for content by two university professors of moral philosophy (see 'Acknowledgements' section). The text of these dilemmas is provided in Supplementary Table 1. The number of utilitarian responses and response times for each condition were compared using a general linear model procedure to delineate group differences in SAS 9.2. As a greater proportion of control subjects were female, gender was included in each of our models as an independent variable.

Participants performed the moral reasoning task while supine in the scanner; they viewed a screen through a mirror and listened to audio stimuli through padded headphones, and held a fibre-optic response pad in their right hand (with their index and middle fingers on the left and right buttons, respectively). There were three functional runs, each 420 s in duration. During each run, subjects were presented with seven dilemmas; across all three runs, the dilemmas were presented in a pseudorandomized order. Stimuli were presented and responses were recorded using E-prime (Psychology Software Tools, Inc). This was followed by T_1 structural neuroimaging; in control subjects this was followed by an 8 min resting-state functional MRI scan.

Neuroimaging acquisition

Neuroimaging data were collected on a Siemens 3 T Trio scanner. For the blood oxygen level-dependent functional MRI task paradigm, 630 T_2*-weighted echo-planar volumes were acquired with the following parameters: 29 anterior commissure-posterior commissure aligned axial slices in interleaved order; slice thickness = 3.0 mm with 15% gap; field of view 230 × 230 mm; matrix = 128 × 128; repetition time = 2000 ms; echo time = 28 ms; flip angle = 77°. For the blood oxygen level-dependent functional MRI resting-state paradigm, 240 T_2*-weighted echo-planar volumes were acquired with the following parameters: 36 anterior commissure-posterior commissure aligned axial slices in interleaved order; slice thickness = 3.0 mm with 20% gap; field of view 230 × 230 mm; matrix = 92 × 92 mm; repetition time = 2000 ms; echo time = 27 ms; flip angle = 80°.

For intersubject registration and voxel-based morphometry, a T_1-weighted 3D MP-RAGE sequence was acquired with the following parameters: 160 sagittal slices; slice thickness = 1 mm; field of view = 256 × 256 mm; matrix = 230 × 256; repetition time = 2300 ms; echo time = 2.98 ms; flip angle = 9°.

Structural neuroimaging analysis

To identify regions of atrophy, the eight subjects with behavioural variant FTD included in the neuroimaging analysis were compared with 48 normal control subjects (the 16 control subjects who took part in the functional study, plus 32 additional age- and gender-matched control subjects) with voxel-based morphometry. Structural T_1 images were initially normalized in SPM5, and more anatomically precise intersubject registration was performed with the Diffeomorphic Anatomical Registration through Exponential Lie Algebra (DARTEL) procedure (Ashburner, 2007). Subjects with behavioural variant FTD were compared with control subjects, covarying out age, gender and total intracranial volume, and all statistical maps were thresholded at voxelwise $T > 4.61$ to obtain a study-specific family-wise error threshold based upon a Monte Carlo simulation running 1000 permutations.

Functional magnetic resonance imaging univariate task activation analysis

Prior to preprocessing, all raw data were visually inspected and volumes with excessive head motion (visible interleaving artefact) or other artefacts were excluded. The number of volumes excluded was 20.0 ± 21.5 in patients with behavioural variant FTD and 3.8 ± 7.0 in control subjects. Functional MRI data were then preprocessed using standard methods in SPM5. Functional images acquired during the moral reasoning task were corrected for slice timing differences, realigned to account for within-scan head movement, unwarped to minimize susceptibility-by-movement interactions, smoothed with an 8 mm Gaussian filter, and high-pass filtered (cut-off = 128 s) to remove slow signal drift.

In our analysis, we sought to model the time period during which subjects deliberated about the moral decision. Based upon pilot testing and on observation of subjects' response times (in which subjects often responded immediately after question presentation, suggesting that they had already thought about how they would respond prior to hearing the question), we modelled this deliberation period as including the second half of the vignette presentation and the first 8 s of the question and response period [to include the mean + 1 standard deviation (SD) of the response time]. The design matrix included one explanatory variable for each of the three conditions, consisting of a boxcar function convolved with a haemodynamic response function. Several nuisance regressors were also included. The first nuisance variable, common to all three conditions, was used to model auditory, visual and language processing during the first half of the vignette. Additional covariates of no interest were included to reduce error variance: six movement parameters (three translation and three rotation parameters saved during realignment) and raw signal time courses from grey matter, white matter and CSF regions of interest. We then fit a voxel-wise general linear model to the blood oxygen level-dependent signal time course for each regressor in each participant using standard parameters [Restricted Maximum Likelihood and an autoregressive AR(1) model to correct for non-sphericity arising from serial correlations].

Random effects analyses were performed on contrast images from individual subjects, which were normalized to MNI space using the transformations derived with Unified Segmentation and DARTEL described above. Age, gender and head motion (using the root mean square of each individual's scan-to-scan translational movement in millimetres) were included as additional covariates of no interest. All contrasts were conducted across the whole brain, thresholded at voxelwise $P < 0.001$ and corrected for multiple comparisons at $P < 0.05$ based on cluster extent according to Gaussian random field theory.

Granger causality analysis

The univariate comparison between patients and control subjects (findings described below) was consistent with our hypothesis of causal influence from the salience network to the default mode network during moral reasoning. We sought further support for this hypothesis by applying Granger causality analysis, a multivariate analytic method that characterizes directional functional connections among brain regions. Granger causality analysis is based on the intuitive inference that x causes y if knowing x helps to predict the future of y. More specifically, a time series x 'Granger causes' a time series y if including past observations of x reduces the prediction error of y in a linear regression model of x and y, compared with a model that includes only past observations of y (Roebroeck *et al.*, 2005; Kayser *et al.*, 2009; Seth, 2010). The magnitude of this relationship ($F_{x\to y}$) in a bivariate analysis is expressed as the log ratio of the prediction error variances of the model including only y and of the model including x and y. This logic can be extended to a multivariate analysis, in which case the Granger causal influence from x to y, conditioned on any additional time series, is expressed as the log ratio of the prediction error variances of the model of y including every time series except x and of the model with every time series including x. It should be noted that 'Granger causal' influences (like all measures of directed functional connectivity) may not be equivalent to physical causal interactions, and may be better understood as statistical relationships characterizing the flow of information across different series of observations (Seth, 2010).

We designed our Granger causality analysis to test for causal interactions among the salience network, default mode network and executive control network; as described in the Supplementary material, we identified two primary nodes within each of these three canonical networks as regions of interest for Granger causality analysis (Sridharan *et al.*, 2008). Estimates of Granger causal influence ($F_{x\to y}$) among these six regions were computed using the Causal Connectivity Toolbox (Seth, 2010). Connections with a dominant direction of influence were identified using the difference of influence measures in either direction ($F_{x\to y} - F_{y\to x}$). We used bootstrapping techniques, block-randomizing time series to generate an empirical null distribution of Granger causal influence measures and their differences for statistical inference using functional MRI data from normal control subjects. Statistically significant Granger causal influences across subjects were identified using a Wilcoxon rank-sum test at a stringent threshold ($P < 0.01$, Bonferroni corrected). Use of the difference of influence measure for dominant directed influences allowed for a less stringent statistical threshold ($P < 0.05$, Bonferroni corrected) for these links. In a bivariate (frontoinsular→posterior cingulate cortex) analysis, Granger causal influence measures computed from normal control subjects and patients with behavioural variant FTD were compared using a Wilcoxon rank-sum test at $P < 0.05$, Bonferroni corrected.

Results

Atrophy in patients with behavioural variant frontotemporal dementia

The most markedly atrophic region in patients with behavioural variant FTD was an extensive contiguous anterior region including the bilateral striatum, orbitofrontal cortex, anterior insula, anterior temporal lobe (including amygdala), anterior cingulate cortex and frontal pole. Other foci of atrophy were found through the frontal and temporal lobes (Fig. 1 and Table 2). These regions have been characterized in previous studies as sites of atrophy in the earliest stages of behavioural variant FTD (Rosen *et al.*, 2002; Broe *et al.*, 2003; Seeley *et al.*, 2008). Many of these regions, particularly the anterior cingulate, anterior insula, orbitofrontal cortex and ventral striatum, are core nodes of the salience network.

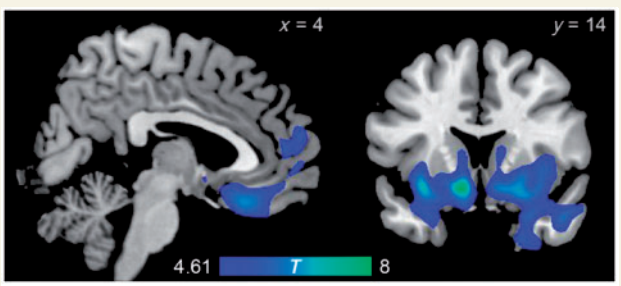

Figure 1 Regions with significantly reduced volumes in patients with behavioural variant FTD relative to normal control subjects, as revealed by voxel-based morphometry.

Table 2 Regions of significant atrophy in the behavioural variant FTD group

Region	x	y	z	Extent (mm^3)	max *T*
Bilateral ventral striatum, orbitofrontal cortex, anterior insula, anterior temporal lobe, anterior cingulate cortex, frontal pole	−10	14	−12	102 760	8.21
Right superior frontal sulcus	20	26	44	352	5.17
Right orbital sulcus	28	36	−14	320	5.19
Left orbital sulcus	−26	34	−14	128	4.88
Left middle temporal gyrus	−60	−6	−12	104	4.88
Genu of corpus callosum	−4	34	2	88	4.83
Left inferior temporal gyrus	−48	−36	−22	40	4.87
Left middle temporal gyrus	−60	8	−20	16	4.68

T statistics are thresholded based upon a Monte Carlo simulation running 1000 permutations.

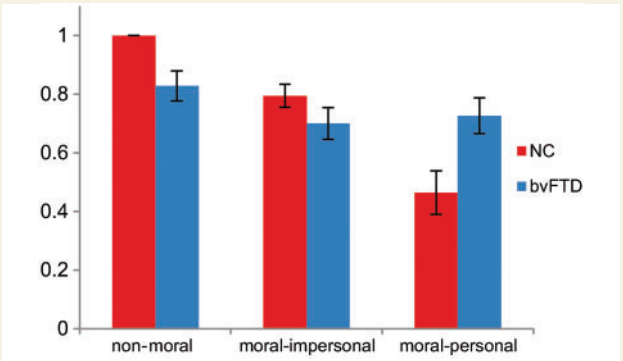

Figure 2 Proportion of utilitarian responses to non-moral, moral–impersonal, and moral–personal dilemmas in control subjects and patients. Error bars refer to the standard error of the mean. NC = normal control subjects; bvFTD = behavioural variant FTD.

Abnormally utilitarian moral reasoning in behavioural variant frontotemporal dementia

In non-moral practical dilemmas, patients with behavioural variant FTD made fewer utilitarian (in these dilemmas, personally advantageous) decisions than control subjects (83% versus 100%, $P = 0.0003$). In impersonal moral dilemmas, utilitarian decisions did not differ across groups (70% versus 80%, $P = 0.16$). In personal moral dilemmas, patients with behavioural variant FTD were more likely than control subjects to endorse utilitarian violations of personal rights (73% versus 46%, $P = 0.022$). (Fig. 2 and Supplementary material)

We observed a difference between patients and control subjects in responses to non-moral practical dilemmas, likely reflecting broader impairments in semantic processing and practical reasoning in our behavioural variant FTD cohort. To ensure that the abnormal utilitarian responses to personal moral dilemmas were not driven by these more general impairments in language and judgement, we generated an additional model incorporating subjects' responses to non-moral and moral–impersonal dilemmas as well as sex as potential confounds. In this model, the difference between patients with behavioural variant FTD and control subjects remained significant ($P = 0.041$), indicating that abnormal responses to personal moral dilemmas in behavioural variant FTD are not fully explained by generic deficits in language or practical reasoning.

Healthy older subjects recruit the default mode network during personal moral reasoning

In healthy older control subjects, no regions demonstrated significantly different patterns of activation between non-moral and moral–impersonal dilemmas. Several regions were more activated by moral–personal dilemmas than by either non-moral or moral–impersonal dilemmas, including the precuneus/posterior cingulate cortex, right angular gyrus and medial prefrontal cortex. These regions overlapped with the default mode network, as defined by a separate independent components analysis of resting-state functional MRI data from the same control subjects (Fig. 3 and Tables 3 and 4). Meanwhile, dorsal frontoparietal regions in the executive control network were less activated by moral–personal dilemmas than by either non-moral or moral–impersonal dilemmas (Fig. 4 and Tables 5 and 6). All of these findings are consistent with previous findings in young subjects (Greene *et al.*, 2001).

Default mode network recruitment during personal moral reasoning is diminished in behavioural variant frontotemporal dementia

Comparing the difference in functional activation between the moral–personal and non-moral conditions, a cluster within the bilateral posterior cingulate cortex and precuneus demonstrated a lesser increase in activity during the moral–personal condition in patients with behavioural variant FTD than in normal control subjects (Fig. 5 and Table 7). Atrophy correction was not performed on this comparison because the region of differential recruitment is distant from sites of atrophy in the behavioural variant FTD patient group. No significant between-group differences were observed when comparing the difference in functional activation between the moral–impersonal and non-moral conditions, or between the moral–personal and moral–impersonal conditions. Refer to the Supplementary material for further discussion.

The salience network exerts Granger causal influence on the default mode network during moral reasoning

Our finding that patients with behavioural variant FTD with atrophy in the salience network have reduced functional MRI recruitment in the medial parietal default mode network supports the hypothesis that the salience network causally influences the default mode network during personal moral dilemmas. More broadly, cognitive states that activate the default mode network typically deactivate the executive control network, and vice versa, and existing evidence supports a general role for the salience network in switching between these two networks in response to task demands (Rilling *et al.*, 2008; Sridharan *et al.*, 2008; Menon and Uddin, 2010; Bonnelle *et al.*, 2012). This suggests a model in which the salience network is responsible for default mode network recruitment with executive control network deactivation during personal moral dilemmas and executive control network recruitment with default mode network deactivation during non-moral and impersonal moral dilemmas. An alternative explanation is that because our behavioural variant FTD cohort also had atrophy in the medial prefrontal cortex node of the default mode network, dysfunction in this frontal node may have contributed to

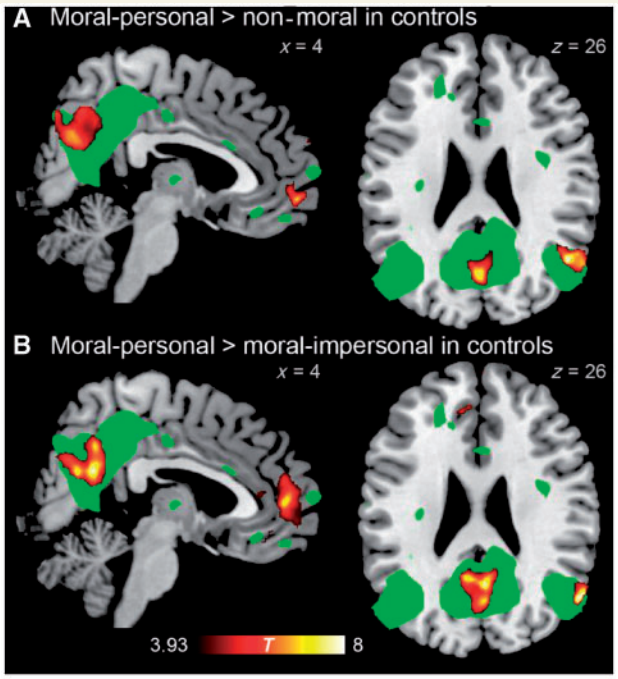

Figure 3 Brain regions demonstrating greater activity for moral–personal than for (**A**) non-moral dilemmas, and than for (**B**) moral–impersonal dilemmas in normal control subjects. For comparison, the default mode network as identified in resting state functional MRI from 15 control subjects is displayed in green at voxel-wise $P = 0.0001$.

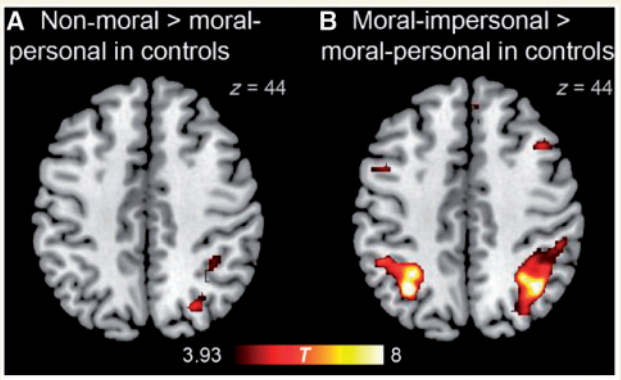

Figure 4 Brain regions demonstrating greater activity for (**A**) non-moral than for moral–personal dilemmas, and for (**B**) moral–impersonal than for moral–personal dilemmas in normal control subjects.

Table 3 Brain regions demonstrating greater activity for moral-personal than non-moral dilemmas in control subjects

Region	*x*	*y*	*z*	Extent (mm^3)	*P*	max *T*
Right angular gyrus	50	−60	26	3000	<0.001	8.46
Precuneus/posterior cingulate cortex	0	−78	42	9776	<0.001	8.30
Ventromedial prefrontal cortex, frontal pole	8	60	−4	3016	<0.001	7.99

P-values are corrected based on cluster extent, whereas max *T* is the *T* statistic of each local maximum.

Table 4 Brain regions demonstrating greater activity for moral-personal than moral-impersonal dilemmas in control subjects

Region	*x*	*y*	*z*	Extent (mm^3)	*P*	max *T*
Ventromedial prefrontal cortex, anterior cingulate cortex, frontal pole	−4	34	−14	9912	<0.001	8.28
Right angular gyrus	56	−64	26	1776	<0.001	8.27
Precuneus/posterior cingulate cortex	4	−58	24	9184	<0.001	8.21
Left putamen, globus pallidus	−20	4	−12	992	0.009	5.86

P-values are corrected based on cluster extent, whereas max *T* is the *T* statistic of each local maximum.

Table 5 Brain regions demonstrating greater activity for non-moral than moral–personal dilemmas in control subjects

Region	x	y	z	Extent (mm^3)	P	max T
Right extrastriate occipital cortex	34	−84	16	3376	<0.001	7.53
Left extrastriate occipital cortex	−22	−96	4	1512	0.002	7.08
Right middle frontal gyrus	40	−2	62	856	0.041	4.27
Right superior parietal lobule	36	−46	48	2136	<0.001	5.57
Left precentral gyrus	−34	−24	66	1192	0.009	5.49

P-values are corrected based on cluster extent, whereas max *T* is the *T* statistic of each local maximum.

Table 6 Brain regions demonstrating greater activity for moral–impersonal than moral–personal dilemmas in control subjects

Region	x	y	z	Extent (mm^3)	P	max T
Left superior parietal lobule	−32	−60	44	6776	<0.001	12.63
Right superior parietal lobule	40	−58	46	12 752	<0.001	10.28
Left middle frontal gyrus	−36	14	30	3832	<0.001	9.60
Right inferior frontal sulcus	46	38	14	3880	<0.001	9.38
Left extrastriate occipital cortex	−26	−72	30	880	0.001	8.03
Right superior frontal gyrus	8	0	52	2680	<0.001	7.97
Right middle frontal gyrus	44	20	40	2992	<0.001	7.47
Right paracingulate gyrus	4	26	48	976	0.011	7.40

P-values are corrected based on cluster extent, whereas max *T* is the *T* statistic of each local maximum.

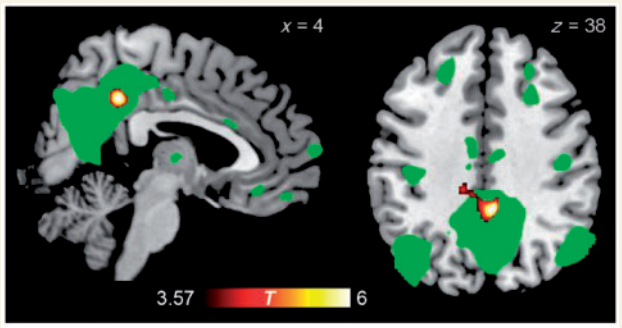

Figure 5 Brain regions demonstrating greater contrast between moral–personal and non-moral dilemmas in control subjects than in patients with behavioural variant FTD. For comparison, the default mode network as identified in resting-state functional MRI from 15 control subjects is displayed in green at voxel-wise $P = 0.0001$.

Table 7 Brain regions demonstrating greater contrast between moral–personal and non-moral dilemmas in control subjects than in patients with behavioural variant FTD

Region	x	y	z	Extent (mm^3)	P	max T
Posterior cingulate/ precuneus	4	−42	38	2112	0.003	6.84

P-values are corrected based on cluster extent, whereas max *T* is the *T* statistic of each local maximum.

abnormal recruitment of the posterior cingulate cortex node of the default mode network.

To elicit evidence for either of these hypotheses, we used Granger causality analysis to characterize directed interactions between nodes of these networks while healthy subjects performed the moral reasoning task. Using time series extracted from two primary nodes each from the salience network, default mode network and executive control network, we generated a network map representing directed functional connections between these nodes (Fig. 6 and Table 8). Granger causality analysis uncovered dominant directed influences from the salience network to the default mode network and the executive control network; including from a right frontoinsular node of the salience network to a posterior cingulate cortex node of the default mode network with reduced recruitment during personal moral reasoning in patients with behavioural variant FTD, and also from an anterior cingulate cortex node of the salience network to the medial prefrontal cortex node of the default mode network. In addition, we analysed network properties of each node during the moral reasoning task, constructing a map of Granger causal influences in each subject (links at $P < 0.01$, Bonferroni corrected) for a network analysis. This analysis demonstrated that the right frontoinsular is a causal outflow hub of the network, with the highest number of causal outflow connections (out degree) and the highest net causal outflow in control subjects (out–in degree; Supplementary Fig. 1 and Supplementary Table 2A).

Granger causal influence from the salience network to the default mode network is diminished in behavioural variant frontotemporal dementia

We then performed Granger causality analysis on time series extracted from functional MRI data from the eight patients with behavioural variant FTD in our neuroimaging analysis. We found no significant differences between the Granger causality analysis influences observed in patients with behavioural variant FTD and healthy control subjects in a multivariate analysis using six nodes to represent three canonical networks. In multivariate Granger causality analysis, the inclusion of more nodes may reduce the potential informativeness of each individual time series in predicting the other time series, which would make between-group differences in Granger influence more difficult to discern. To detect more subtle differences in Granger influence, we performed bivariate Granger causality analysis using only the frontoinsular and posterior cingulate cortex nodes. In healthy control subjects, this analysis revealed significant bidirectional Granger influences, again with a dominant direction of influence from the frontoinsular cortex to the posterior cingulate cortex. In this bivariate analysis, the Granger influence from the frontoinsular cortex to the posterior cingulate cortex was reduced in patients with behavioural variant FTD compared with control subjects (median 0.0161 versus 0.0448, $P = 0.016$). Refer to the Supplementary material for further discussion. Finally, in an analysis of network properties the right frontoinsular cortex was also the only node with significantly disrupted inflow and outflow network properties in patients with behavioural variant FTD (Supplementary Table 2B; out degree $P = 0.043$, in degree $P = 0.022$; one-tailed t-test not corrected for multiple comparisons).

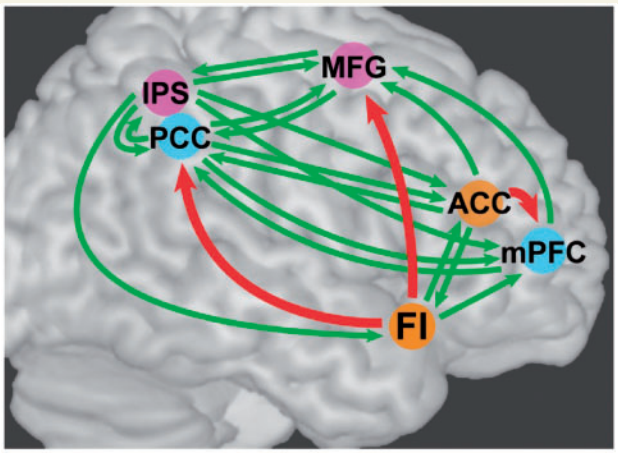

Figure 6 Granger causality analysis of key nodes of the salience (orange), default mode (blue), and executive control (pink) networks during the moral reasoning task. Connections with significant Granger influences at the group level (Wilcoxon rank-sum test, $P < 0.01$, Bonferroni corrected) are depicted in green; a subset of these connections with a dominant direction of influence (Wilcoxon rank-sum test, $P < 0.05$, Bonferroni corrected) are depicted in red. ACC = anterior cingulate cortex; FI = frontoinsular; IPS = intraparietal sulcus; MFG = middle frontal gyrus; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex.

Individual relationships among neuroimaging and behavioural measures

In addition to group-level differences between patients with behavioural variant FTD and normal control subjects, we also explored relationships between measures of behaviour, univariate functional MRI activation and Granger causal influence across individual subjects. As noted above, patients with behavioural variant FTD had diminished Granger causal influence in a bivariate analysis from the frontoinsular cortex to the posterior cingulate cortex, and also had reduced recruitment of the posterior cingulate cortex during personal moral reasoning. Although we did not observe a significant correlation between Granger influence and

Table 8 Granger causal influences across nodes (column→row)

$F_{col->row}$	FI	ACC	mPFC	PCC	MFG	IPS
FI	–	0.0500 ± 0.0136	0.0206 ± 0.0067	0.0141 ± 0.0045	0.0144 ± 0.0042	0.0167 ± 0.0053
ACC	0.0459 ± 0.0149	–	0.0092 ± 0.0022	0.0180 ± 0.0040	0.0249 ± 0.0079	0.0177 ± 0.0040
mPFC	0.0214 ± 0.0047	0.0298 ± 0.0087 ($P = 0.0001$)	–	0.0211 ± 0.0055	0.0083 ± 0.0022	0.0119 ± 0.0027
PCC	0.0309 ± 0.0072 ($P = 0.0007$)	0.0109 ± 0.0023	0.0118 ± 0.0038	–	0.0183 ± 0.0064	0.0252 ± 0.0104
MFG	0.0277 ± 0.0065 ($P = 0.0019$)	0.0163 ± 0.0039	0.0128 ± 0.0033	0.0177 ± 0.0040	–	0.0268 ± 0.0053
IPS	0.0252 ± 0.0069	0.0098 ± 0.0025	0.0132 ± 0.0045	0.0357 ± 0.0122	0.0281±0.0063	–

Cells coloured in green represent directed functional connections that significantly differ from the null distribution at a stringent threshold of $P < 0.01$ corrected for 30 comparisons. Cells outlined in red represent dominant directed influences that significantly differ from the null distribution at a threshold of $P < 0.05$ corrected for 15 comparisons.

FI = frontoinsular; ACC = anterior cingulate cortex; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; MFG = middle frontal gyrus; IPS = intraparietal sulcus.

recruitment of the posterior cingulate cortex during personal moral reasoning (i.e. the difference in activation between the moral–personal and non-moral condition), we did observe a correlation between Granger influence and the beta estimate of posterior cingulate cortex activation during personal moral reasoning alone (Spearman's rho = 0.47, $P = 0.022$; Supplementary Fig. 2).

We found weaker evidence for correlations between individual behaviour and individual neuroimaging measures. As predicted by group findings across patients and normal control subjects, there was a negative correlation between the proportion of utilitarian choices and the beta estimate of posterior cingulate cortex activation during personal moral reasoning (Pearson's $r = -0.37$, one-tailed $P = 0.036$). There was also a trend towards a negative correlation between the proportion of utilitarian choices and Granger influence (in a bivariate analysis) from the frontoinsular cortex to the posterior cingulate cortex. Using a median split to dichotomize participants into more and less utilitarian moral reasoners, the less utilitarian reasoners had greater measures of Granger influence (median 0.0490 versus 0.0181, one-tailed $P = 0.032$).

Discussion

We present here four converging lines of evidence incorporating behavioural, univariate functional neuroimaging, and multivariate functional neuroimaging methods, in both patients and healthy control subjects, which together support a causal influence from the salience network to the default mode network during moral reasoning. First (as previously reported), healthy subjects recruit the default mode network when deliberating about personal moral dilemmas, yet patients with behavioural variant FTD, whose disease preferentially targets the salience network, give abnormally utilitarian responses to these dilemmas. Second, patients with behavioural variant FTD have reduced recruitment of the default mode network compared with normal control subjects when deliberating about these dilemmas. Third, Granger causality analysis of functional MRI data from normal control subjects indicates that nodes of the salience network exert directed influence on nodes of the default mode network during performance of a moral reasoning task. Fourth, this directed functional connectivity from the salience network to the default mode network is diminished in patients with behavioural variant FTD. This causal hypothesis resolves an apparent discrepancy between patient-based and activation-based studies of moral reasoning, and coheres with other studies that support a causal role for the salience network in modulating default mode network activity in response to task demands. One recent study used chronometric and Granger causality analysis techniques to indicate that the salience network (especially the right frontoinsular cortex) plays a critical role in switching between default mode network and executive control network during both task-related and resting states (Sridharan *et al.*, 2008). Another Granger causality analysis analysis using a socially interactive task indicated that the bilateral frontoinsular and anterior cingulate cortex causally influence the medial prefrontal node of the default mode network, with greater influence during a social condition than during a non-social control condition (Rilling *et al.*, 2008). And in a study of patients with traumatic brain injury, aberrant default mode network deactivation during an attention-demanding task was specifically predicted by loss of fractional anisotropy in the white matter tract between the right frontoinsular cortex and anterior cingulate cortex (Bonnelle *et al.*, 2012).

The present study extends these earlier findings by combining patient-based methods with measures of functional connectivity, and by linking disruption of this causal relationship to salience network-related social and behavioural abnormalities that are characteristic of behavioural variant FTD (Zhou *et al.*, 2010). Discovering causal relationships between large-scale networks in the setting of neurodegenerative diseases that target particular networks is likely to be crucial in advancing our understanding of how these and other diseases produce cognitive effects in distant, interconnected brain regions. Unfortunately, inferential support for such causal hypotheses using patient studies or activation data is almost always indirect, relying upon methodological and neuroscientific assumptions that are open to question. We believe that the convergence of findings from different methods is a strength of this study, as different findings rely upon different assumptions.

To make these assumptions explicit, one finding in support of our hypothesis is that patients with behavioural variant FTD with atrophy in the salience network have reduced recruitment of the posterior cingulate cortex node of the default mode network during personal moral reasoning as compared with healthy control subjects. An interpretive difficulty often encountered in univariate comparisons of functional MRI activity between patients and control subjects is that activation differences may be confounded by haemodynamic, metabolic or other uncontrolled local physiological differences between groups, aside from the neural difference of interest (D'Esposito *et al.*, 2003). This concern is mitigated in the present study by the fact that the posterior cingulate cortex is distant from sites of regional atrophy in our patient cohort (Fig. 1). However, there may also have been true neural differences in recruitment (for instance, in the medial prefrontal node of the default mode network, which was also atrophied in our patient cohort) that we were unable to detect due to these physiological confounds.

Another finding in support of our hypothesis is the network map (Fig. 6) generated by our Granger causality analysis of functional MRI data from healthy older control subjects during the moral reasoning task. This finding does not involve patient data or on group differences, and so does not rely on the same assumptions as the univariate finding. Granger causality analysis and a related analytical technique, dynamic causal modelling, are two broadly used methods for discovering directed influences using functional MRI data (Valdes-Sosa *et al.*, 2011); dynamic causal modelling was not appropriate to our task because the temporal properties of each vignette relevant to moral reasoning could not be precisely specified in advance. The methodological literature on Granger causality analysis has focused on two potential difficulties: regional differences in haemodynamic lag and downsampling. To illustrate the first problem, functional MRI blood oxygen level-dependent signal measures blood oxygenation rather than neural activity directly, so in theory if the haemodynamic response to neural activity in region x is faster than in region y, the blood oxygen level-dependent time course in region x could 'predict' the blood

oxygen level-dependent time course in region *y* even if neural events in both regions are concurrent (or even if neural events in *y* precede those in *x* but by less than the difference in haemodynamic lag). Several studies using simulations and actual functional MRI data have been performed to evaluate this possibility, with some indicating that Granger influences in functional MRI studies are therefore vulnerable to spurious findings (David *et al.*, 2008; Smith *et al.*, 2011), and others indicating that the method is robust enough that significant Granger influences are unlikely to be attributable solely to such confounds (Deshpande *et al.*, 2010; Schippers *et al.*, 2011; Seth *et al.*, 2013). To illustrate the second problem, whereas neural events occur on a millisecond timescale, data acquisition in functional MRI typically occurs on a second timescale (the repetition time in our study was 2 s). The information lost in downsampling increases the prediction error of *y* in a linear regression model including past observations of *y*; but if *x* and *y* are correlated (even if because *y* causally influences *x*), then some of *y*'s lost information can be reintroduced by including *x* in the model, reducing the prediction error of *y* without reflecting a true directed influence from *x* to *y* (Roebroeck *et al.*, 2005; Seth *et al.*, 2013). For our main Granger causality analysis finding we used the difference of influence measures in either direction ($F_{x\rightarrow y} - F_{y\rightarrow x}$), which is standardly applied to avoid spurious directionality due to downsampling (Roebroeck *et al.*, 2005). Still, given these ongoing methodological controversies, we regard this Granger causality analysis as offering additional evidence in favour of our hypothesis, rather than as decisive on its own.

Finally, we found that Granger causal influence from the frontoinsular to the posterior cingulate cortex during moral reasoning was diminished in patients with behavioural variant FTD. This finding may unify the findings of our univariate comparison between patients and control subjects with the findings of our Granger causality analysis in control subjects, although the interpretation of this finding does depend on many of the same assumptions as these other two findings. In particular, the frontoinsular node used in our Granger causality analysis is based on a local statistical peak of atrophy in the behavioural variant FTD cohort (as detailed in the Supplementary material). It is possible that the reduced Granger causal influence and disrupted network properties of this node in patients (Supplementary Table 2B) reflect reduced fidelity of the functional MRI blood oxygen level-dependent signal due to atrophy or other regional physiological confounds, rather than alterations of neural activity itself. This concern applies not only to the present finding, but also to many other functional MRI studies of functional connectivity or network properties in brain regions affected by disease. We note also that neuronal loss and local physiological derangements likely are not independent from neural dysfunction, but instead are likely to be related and in some respects, causative. Here again, we believe that the most important observation is that this finding supports the same causal hypothesis as our other findings.

A revised two-process model of moral judgement

Earlier functional MRI studies of personal moral reasoning were initially thought to support a dual process model of moral judgement, in which a cognitive/rational system subserves utilitarian moral reasoning and an emotional system subserves counter-utilitarian moral reasoning (Greene *et al.*, 2001, 2004). This interpretation was based on the claim that the precuneus/posterior cingulate cortex, lateral parietal cortex and medial prefrontal cortex, which are recruited during personal moral judgement, are specifically involved in emotion processing. However, subsequent research indicates that what unifies these regions is not a shared relationship to emotional processing (though the medial prefrontal cortex does subserve emotional processes that likely are relevant to moral reasoning), but instead that they are nodes of the default mode network (Harrison *et al.*, 2008). Furthermore, more detailed analysis of reaction time data used to support the model does not support the proposed interpretation (McGuire *et al.*, 2009).

Although current evidence does not support the claim that personal moral judgement involves a conflict between specifically emotional and rational processes, it remains notable that the default mode network is more activated by moral–personal than by non-moral or moral–impersonal dilemmas, while the executive control network is more activated by non-moral and moral–impersonal than moral–personal dilemmas. The differential engagement of these two networks does suggest that two distinct cognitive processes may be engaged by moral reasoning, and that they respond differently based on the content of the moral problem under consideration.

Given previous research that implicates the salience network in attention, alertness and in switching between the default mode network and executive control network (Dosenbach *et al.*, 2006; Seeley *et al.*, 2007; Sridharan *et al.*, 2008; Menon and Uddin, 2010; Nelson *et al.*, 2010), we suggest that the salience network plays an alerting and switching role during moral reasoning. In personal moral dilemmas, the salience network utilizes social and emotional resources to identify the personal nature of these dilemmas and then recruits the default mode network; whereas in other decisions, the salience network recruits the executive control network. This model predicts that in behavioural variant FTD, salience network dysfunction will result in failure to recognize the personal nature of these dilemmas, which in turn leads to a failure to appropriately recruit the non-targeted default mode network. The behavioural manifestation of these abnormal relationships between networks would be a tendency to deliberate about personal moral dilemmas in a manner analogous to the way healthy control subjects deliberate about non-moral and impersonal moral dilemmas, where personal rights are not at stake.

If the default mode network as a network does not specifically subserve emotional processing, the question remains why it is recruited in moral dilemmas with personal content. We note that one feature that unifies many of the cognitive operations that engage the default mode network—such as retrieving autobiographical memories, envisioning the future, navigating spatial environments, and inferring other people's states of mind—is that they involve the construction of dynamic mental simulations of states of affairs that are not presently available in sense experience (Tulving, 1983; Suddendorf and Corballis, 1997; Buckner *et al.*, 2008; Spreng and Grady, 2010). One link with moral reasoning may be that in personal, more than impersonal moral dilemmas, the deliberator must often simulate the subjective

points of view of the agent or of other affected parties. For example, in the case of an impersonal moral dilemma, if a policy would be better for many people and worse (to an equivalent degree) for a few, it would be natural to decide in favour of this policy on the basis of expected utility, without engaging in a mental simulation of any affected person's point of view. However, when deliberating about whether to push an innocent person into the path of a trolley that would otherwise kill five, it is natural to imagine 'what it would be like' to push the innocent person, or to be the person pushed, or to be one of the five that would be saved.

The default mode network's role in mental simulation may provide a neuroscientific framework for the philosophical claim that counter-utilitarian moral reasoning is closely tied to a personal point of view, while utilitarian moral reasoning is tied to an objective conception of the world without reference to any individual perspective. For instance, Rawls (1971) argued that utilitarianism does not properly account for the distinctness of persons; Nagel (1986) proposed an account of personal rights that appeals to the perspective of the moral agent, and Kamm (1992) has developed an alternative that appeals to the perspective of the person whose rights are violated. If deliberation about personal rights requires one to adopt a personal point of view, one role of the default mode network in personal moral reasoning may be to access different relevant points of view (both of the agent and of those affected by the action) by mental simulation. Conversely, the executive control network would be engaged by judgements that do not require such a simulation, such as those non-moral and impersonal moral dilemmas that can be resolved by a calculation of expected utilities.

In summary, our findings reconcile a discrepancy between previous activation-based and patient-based studies of the role of the default mode network in moral reasoning, and suggest a revision to an influential dual-process account of moral reasoning. While our model has been developed using findings from behavioural variant FTD, the model has implications for other socio-emotional disorders associated with abnormalities in personal moral judgement such as psychopathy (Pujol *et al.*, 2011), medial prefrontal structural brain lesions (Ciaramelli *et al.*, 2007; Koenigs *et al.*, 2007), alcoholism (Khemiri *et al.*, 2012), and autism (Gleichgerrcht *et al.*, 2012), particularly as evidence accumulates that all of these disorders may involve disruption of the salience network (Bjork *et al.*, 2008; Di Martino *et al.*, 2009; Nomura *et al.*, 2010; Ly *et al.*, 2012; von dem Hagen *et al.*, 2012). In all of these disorders, a central question concerns the functional interrelationship between networks that are targeted by disease and networks that are relatively spared. Our findings contribute to existing research indicating a central role for the salience network in modulating and regulating the activity of other large-scale networks such as the default mode network, which may help to explain the profound behavioural consequences of injury to the salience network in behavioural variant FTD and other disorders.

Limitations

Our study was limited in the number of subjects with behavioural variant FTD available for study (as the extensive cognitive demands of the task limited recruitment to patients in the earliest stages of disease) and also in the number of trials available for each subject (given reduced patient tolerance for testing and the long trials required by our vignette-based paradigm). This precluded potentially informative analyses, such as comparisons between activation preceding utilitarian and non-utilitarian responses within each condition, or comparisons between utilitarian responses to moral–personal dilemmas in patients and control subjects.

Given difficulties inherent to functional MRI in patient populations, and in matching disease cohorts to healthy cohorts, we chose to focus this study on moral reasoning in behavioural variant FTD and did not include an Alzheimer's disease comparison group. It remains unclear why patients with Alzheimer's disease and atrophy in the default mode network give normal responses to these dilemmas; one potential explanation is that the medial prefrontal cortex node is less affected than more posterior nodes of the default mode network in Alzheimer's disease. This node may serve as a transition zone between the default mode network and salience network given its functional connectivity with orbitofrontal and ventral striatal regions involved in salience processing (Greicius *et al.*, 2003) and its involvement in socio-emotional reasoning (Amodio and Frith, 2006). Future studies of activation and network dynamics during moral reasoning in early Alzheimer's disease may be useful in evaluating this hypothesis, and may help to clarify the cognitive contributions and interrelationships of different subsystems within the default mode network (Andrews-Hanna *et al.*, 2010).

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Supplementary material

Supplementary material is available at *Brain* online.

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The salience network causally influences default mode network activity during moral reasoning:
Supplementary Materials: Tables (3); Figures (4)

Supplementary Methods

Moral reasoning task stimuli

The classification of dilemmas into three conditions was based upon a distinction between "impersonal" and "personal" moral dilemmas applied in earlier work (Greene *et al.*, 2001; Greene *et al.*, 2004; Koenigs *et al.*, 2007), but with modifications. The original distinction appealed to a hypothesized psychological mechanism, and by design did not incorporate any philosophical account of the distinction between these two types of judgment (such as an appeal to personal rights). "Personal" moral dilemmas were originally characterized as involving acts that are (i) likely to cause serious bodily harm, (ii) to a particular person, (iii) and not merely from the deflection of an existing threat onto a different party (Greene *et al.*, 2001; Greene and Haidt, 2002); while "impersonal" dilemmas concerned acts that lack at least one of these features. However, this distinction has been widely criticized.

First, this version of the personal/impersonal distinction failed to distinguish between two very different kinds of situation: true "personal" moral dilemmas in which a violation meeting these three conditions is necessary to produce an objectively good outcome (e.g., pushing one person into the path of a trolley that would otherwise kill five), and other cases in which such a violation would produce a purely selfish outcome (e.g., killing someone to collect a life insurance claim). The latter cases are not true moral dilemmas, and the process of deliberating about such cases is not only philosophically, but also cognitively quite different from deliberating about the former cases. Second, given this heterogeneity it cannot be claimed that willingness to commit personal harms reflects utilitarian moral reasoning (Greene *et al.*, 2004; Koenigs *et al.*, 2007; Greene, 2007). While utilitarianism licenses harms that produce good overall outcomes, Greene's original distinction

makes no reference to outcomes, and many of the "personal" scenarios used by Greene and others involve harms that produce selfish or neutral rather than objectively good outcomes. In addition to the personal/impersonal distinction, Greene's dilemmas also incorporated other potentially morally relevant considerations; for instance, many of the putatively personal moral dilemmas involved potential harms to subjects' family members or close friends (Schaich Borg *et al.*, 2006). Other cognitive demands were poorly controlled between dilemmas; for instance, Greene's set of personal dilemmas had greater word length than his set of impersonal dilemmas (Moore, Clark and Kane, 2008). A group of five moral philosophers reviewed Greene's dilemma set, and found that only 45% of impersonal scenarios and 48% of personal scenarios involved a choice between utilitarian and non-utilitarian options (Kahane and Shackel, 2008).

To address these concerns, we created a revised set of dilemmatic vignettes was created, which was reviewed for content by two university professors of moral philosophy. Nonmoral practical dilemmas were characterized as choices that would not materially affect the interests of other people, but in which one option would be better for the agent—for instance, whether to have an old VCR repaired for $100 when an improved and more energy efficient model could be purchased for the same amount. In such cases, the utilitarian choice is also the choice that is best for the individual agent, since (when other people's interests are not affected) this maximizes overall welfare. Impersonal moral dilemmas concerned choices that would substantially affect the interests of other people, and did not involve violating anyone's rights—for instance, whether to vote for a policy that would be worse for a small number of people but better for a large number of people. In these cases, the utilitarian choice is the choice that produces the greatest expected welfare. Personal moral dilemmas concerned choices that would substantially affect the interests of other people, and in which the best overall outcome could only be produced by violating someone's personal rights—for instance, whether to push one person into the path of a runaway trolley that would otherwise kill

five people. Here the utilitarian choice is to sacrifice the lesser number in order to preserve the interests of the greater number, although such choices typically conflict with "commonsense" moral intuitions. These dilemmas were balanced for word length and reading difficulty (Flesch-Kincaid grade level of 6.0 to 7.0); utilitarian responses were also counterbalanced between "yes" and "no" responses to avoid response biases due to impulsivity in bvFTD patients (Mendez and Shapira, 2009). (Supplementary Table 1) These dilemmas were also presented to a separate set of 6 healthy older adults (3 men and 3 women, aged 55-76), who were asked to assess how difficult and how emotionally evocative they found these dilemmas on an ascending 7-point Likert scale. The nonmoral dilemmas were rated as significantly less difficult (1.55) and less emotionally evocative (1.50) than the impersonal moral (difficulty 3.62, $P = 0.003$; emotionality 2.95, $P = 0.012$) and the personal moral dilemmas (difficulty 4.19, $P = 0.003$; emotionality 3.55, $P = 0.017$); differences in ratings for moral-impersonal and moral-personal dilemmas were not statistically significant.

Analysis of fMRI resting state data

In order to compare anatomical patterns of task-based functional activation with the DMN as identified in resting-state functional connectivity, functional MRI data were acquired in the resting state in 15 of our 16 control subjects (1 was not collected due to technical difficulties). Using SPM5, after discarding the first 6 frames to allow for magnetic field stabilization, functional images were corrected for slice timing differences, realigned to account for within-scan head movement, unwarped to minimize susceptibility-by-movement interactions, coregistered with the same subject's task-based fMRI images, and smoothed with an 8mm Gaussian filter. Preprocessed images were concatenated into 4D files and entered into FSL 3.1 Melodic ICA software (http://www.fmrib.ox.ac.uk/fsl/index.html); individual subjects' timecourses were decomposed into 30 independent spatiotemporal components. We then used an automated template-matching

procedure to obtain subject-specific best-fit intrinsic connectivity maps for the DMN (Seeley *et al.*, 2007; Seeley *et al.*, 2009), restricting components to those in which high-frequency signal (>0.1 Hz) constituted less than 50% of the power in the Fourier spectrum. Goodness-of-fit was calculated by comparing each component from each subject to a binarized DMN map derived in earlier work (Damoiseaux *et al.*, 2006). Individual subjects' best-fit ICA components for the DMN were then normalized to MNI space and entered in a random effects analysis using SPM5.

Granger Causality Analysis details

In our GCA analysis, we used timeseries from two primary nodes within each of three canonical networks: the SN, DMN, and ECN. To represent the SN, nodes were derived for the right frontoinsular cortex (FI; centered at 30, 18, -12) and midline anterior cingulate cortex (ACC; 0, 36, 20) based on local statistical peaks of atrophy in the bvFTD cohort (Fig. 1). For the DMN, nodes were derived for the medial prefrontal cortex (mPFC; -6, 52, 8) and posterior cingulate cortex (PCC; 4, -42, 38); these two nodes have been characterized as a midline core of the DMN (Greicius *et al.*, 2003; Andrews-Hanna *et al.*, 2010). The mPFC node was of particular interest to us as node of the DMN that overlaps with regions of atrophy in bvFTD (Fig. 1) and that is functionally connected with orbitofrontal and ventral striatal regions involved in salience processing (Greicius *et al.*, 2003). This node was derived from a local peak of DMN recruitment during personal moral reasoning in healthy subjects (Fig. 3). Meanwhile, the PCC node was derived from the contrast between DMN recruitment during personal moral reasoning in healthy subjects compared to bvFTD patients (Fig. 5). To represent the right-lateralized ECN, nodes were derived for the right middle frontal gyrus (MFG; 29, 3, 56) and intraparietal sulcus (IPS; 36, -46, 48) from overlapping clusters of ECN recruitment during nonmoral and impersonal moral reasoning (Fig. 4).

Mean time-series for 6mm spherical ROIs at each node were extracted using the MarsBar software package (http://marsbar.sourceforge.net). Global signal correction was not performed on these time-series as such techniques may introduce spurious anticorrelations between regions (Murphy *et al.*, 2009; Chang and Glover, 2009; Fox *et al.*, 2009); bandpass-filtering also was not performed as this technique may introduce false positive as well as false negative errors in GCA (Florin *et al.*, 2010; Barnett and Seth, 2011). Linear trends and temporal mean values were removed from time-series for each of the three functional runs at each region to ensure covariance stationarity. Estimates of Granger causal influence ($F_{x \to y}$) among these six ROIs were computed using the Causal Connectivity Toolbox (Seth, 2010). The model order (the number of time-lags included in the model) was selected for each subject using the Bayesian information criterion, and was in each case either 1 or 2.

Supplementary Results

Behavioral differences between bvFTD patients and controls

Prior studies reporting behavioral differences among normal subjects when responding to personal and impersonal moral dilemmas, or interaction effects across healthy and patient cohorts when responding to such dilemmas, have been criticized for failing to exclude the possibility that reported category effects may be driven by idiosyncratic responses to a subset of the dilemmas tested (Kahane and Shackel, 2008; McGuire *et al.*, 2009). In a related criticism, one uncontrolled factor between the personal and impersonal dilemmas used by Greene is intuitiveness—i.e., whether a majority of normal subjects regard a given course of action as morally right (Kahane and Shackel, 2010; Kahane *et al.*, 2012). Given our more stringent characterization of personal and impersonal dilemmas, we examined normal controls' and bvFTD patients' responses to nonmoral, moral-impersonal and moral-personal dilemmas considered individually. (Supplementary Fig. 3A) The

tendency for bvFTD patients to give more utilitarian responses in personal moral dilemmas was observed in all but one of the dilemmas in this category, and was also observed in personal moral dilemmas in which a majority of normal control subjects made a utilitarian choice.

We also examined response time differences between normal controls and bvFTD patients within each dilemma category. (Supplementary Fig. 3B) Patients' response times were slower than controls in nonmoral practical dilemmas (6289ms vs. 5422ms, $P = 0.030$), but did not significantly differ in moral impersonal (6327ms vs. 5958ms, $P = 0.295$) or moral personal dilemmas (6501s vs. 6036s, $P = 0.405$).

Group differences in fMRI activation between bvFTD patients and controls

In the main text results, we report that DMN recruitment during personal moral reasoning is diminished in bvFTD (Fig. 5); this analysis compares the difference between functional activation between the moral-personal and nonmoral conditions across groups, rather than a main effect between groups during the moral-personal condition, to limit confounding due to neurovascular or other physiological differences between groups (D'Esposito, Deouell and Gazzaley, 2003). To examine the basis of this difference in recruitment, we compared beta estimates for functional activation in each of the three conditions (instead of the contrast between conditions) between bvFTD patients and normal controls. During moral-personal dilemmas, a cluster in the right medial parietal lobe (slightly caudal and lateral to the previously observed cluster, also within the DMN) was significantly less activated in bvFTD patients than in normal controls. (Supplementary Fig. 4, Supplementary Table 3) No other group differences in activation were observed in any of the three conditions. This supports the claim that the key difference between patients and controls is a failure to recruit the DMN during personal moral reasoning.

While diminished recruitment during personal moral reasoning was observed between patients and controls when the nonmoral condition was used as a baseline for comparison, no between-group difference was observed when the moral-impersonal condition was used as a baseline for comparison. We investigated this discrepancy by examining the main effect between groups during each condition in a 6mm spherical ROI centered on the peak voxel for diminished DMN recruitment during personal moral reasoning (4, -42, 38), and found evidence for a graded effect across the three conditions. Comparing activation in normal controls to patients, the mean T statistic in this ROI during nonmoral dilemmas was 0.1129, during moral-impersonal dilemmas was 1.7932, and during moral-personal dilemmas was 2.7403. This finding suggests subthreshold differences between bvFTD and normal control subjects in DMN recruitment during impersonal moral dilemmas. One interpretation given our hypothesis in the main text regarding the role of the DMN in mental simulation is that some normal subjects may occasionally engage the DMN when deliberating about some impersonal moral dilemmas as well, particularly since the personal/impersonal distinction may only approximate the actual cognitive or neural difference between these two categories of dilemma (Greene *et al.*, 2001).

Granger causality analyses

As reported in the main text, Granger causal influence from the FI to the PCC in a bivariate model is diminished in bvFTD. While this decline was significant as measured in the primary Granger causal influence measure ($F_{FI \to PCC}$), it was not significant as measured in the more specific difference of influence measure ($F_{FI \to PCC}$ - $F_{PCC \to FI}$, median 0.0009 in bvFTD vs. 0.0149 in controls, $P = 0.561$). Reviewing the data, the decline in the difference of influence measure is less robust than the decline in Granger causal influence because Granger causal influence is also diminished in the reverse direction ($F_{PCC \to FI}$, median 0.0173 vs. 0.0369, $P = 0.232$), consistent with inflow and outflow

dysfunction of the FI in bvFTD. We also considered the alternative possibility that group differences in Granger causal influence from the FI to the PCC might be explained by other uncontrolled differences between groups, such as subject head motion, rather than the neural difference of interest. To evaluate this alternative hypothesis, we compared bivariate GCA for the 14 other node pairs in bvFTD patients and normal controls; none of these other comparisons revealed a statistically significant difference. As uncontrolled nonspecific differences between groups (such as differences in subject head motion) would be expected to affect all node pairs, rather than exert specific effects in a single node pair, this negative finding suggests that the group difference in Granger causal influence from the FI to the PCC is not explained by such non-neural differences between patients and controls.

The GCA incorporated fMRI data from the entire task. We conducted exploratory analyses for changes in Granger causality across different conditions (dilemma types) but found no significant differences, which may reflect the limited number of trials in each condition (as discussed in Limitations). Some authors have advocated looking for changes across conditions as an approach to avoid spurious findings due to interregional differences in hemodynamic lag (Roebroeck, Formisano and Goebel, 2005). We note, however, that such differences across conditions are not predicted by our model, in which the SN causally influences DMN activity in all three conditions.

Supplementary Table 1. Dilemmas used in the modified moral reasoning task.

Category	Dilemma	Word Length	Reading Difficulty	Difficulty	Emotion
nonmoral	You are bringing home some plants from the store. You have lined the trunk of your car with plastic to catch the mud from the plants, but your trunk will not hold all of the plants you have bought. You could bring all of the plants home in one trip, but you would need to put some of the plants in the back seat. If you put the plants in the back seat, the mud from the plants will ruin your fine leather upholstery, which would cost thousands of dollars to replace. Would you make two trips home to avoid ruining the upholstery of your car?	106	6.2	1.7	1.3
	You are at home one day when the mail arrives. You receive a letter from a company that provides financial services. You have heard of this company, which has a good reputation. They have invited you to invest in a mutual fund. The minimum investment for this fund is $1000. You already know a lot about this particular mutual fund. It has performed poorly over the past few years. Based on what you know, there is no reason to think that it will perform any better in the future. Would you invest $1000 in this mutual fund in order to make money?	102	6.8	1.5	1.3
	Your VCR breaks and you bring it to the local repair shop. The woman working in the shop looks at the VCR and tells you that it will cost $100 to fix it. Earlier this morning, you noticed an advertisement in the newspaper. A new model of VCR is available from the same company that made your old VCR. The new model performs the same functions as your old VCR, but is better and uses less electricity. This new VCR is now on sale for $100. Would you have your old VCR fixed instead of spending money on a new one?	101	6.5	1.5	1.5
	You go to the local branch of a busy chain bookstore in order to buy $50 worth of books. You find all of the books that you were looking for, and you are now waiting in line to buy them. You have two coupons with you, and you can use one of them today. One coupon gives you 30% off of your purchase price, and expires tomorrow. The other coupon gives you 25% off of your purchase price, and does not expire for another year. Would you use the 30%-off coupon now so that you will have another coupon to use during the coming year?	105	6.6	1.2	1.3
	You have a very bad headache. You go to the pharmacy looking for your favorite brand of headache medicine. When you get there, you find that the pharmacy is out of the brand that you are looking for. You have known the pharmacist at this store for a long time, and you trust him. He says he has a generic medicine that is "exactly the same" as the name-brand medicine that	100	6.9	2.0	1.5

	you wanted. In the past, he has always given you good advice. Would you keep looking for the name-brand medicine you came for, instead of buying the generic medicine?				
	You need to travel to a nearby city in order to attend a meeting that starts at 2:00 PM. You can either take the train or the bus. The train will get you there just in time for your meeting no matter what. The bus is scheduled to arrive an hour before your meeting. However, the bus sometimes is several hours late because of traffic. It would be nice to have an extra hour before the meeting, but it is very important that you arrive on time. Would you take the train instead of the bus in order to ensure that you are not late for your meeting?	108	6.7	1.7	1.5
	An old friend invites you to spend the weekend at his summer home. This house is up the coast from where you live. You plan to drive, and you can take either the highway or the coastal road. The highway will get you there in about three hours, but the scenery along the highway is very boring. The coastal road will get you to your friend's house in about three hours and fifteen minutes, and the scenery along the coastal road is very beautiful. Would you take the coastal road in order to see the beautiful scenery as you drive?	100	6.7	1.3	2.0
moral impersonal	You work for the Government Health Agency. You must decide whether to promote a new vaccine. This vaccine will protect almost everyone who takes it from a deadly disease. However, the vaccine also carries a risk. A very small number of healthy people who take it will get the disease from the vaccine. You have carefully studied the safety of the vaccine. The chance that someone will die because they did not take the vaccine is much greater than the chance that they will die from the vaccine. Would you tell people to use this vaccine to prevent the disease?	100	6.9	3.0	2.3
	You are the night watchman in a hospital. One night, an accident in the building next door makes deadly chemicals enter the hospital's air ducts. If you don't do anything, these fumes will enter a room with three patients in it, and they will all die. The only way to save these three patients from dying is to hit a certain switch. This will keep the fumes out of the room with the three patients in it. Instead, the fumes will enter a room with a single patient in it, and he will die. Would you allow the fumes to enter the room with three patients so that the single patient will live?	113	6.0	4.0	3.8
	You are the driver of a runaway trolley approaching a fork in the tracks. On the tracks going to the left is a group of five railway workers. On the tracks going to the right is a single railway worker. If you do nothing, the trolley will go to the left, causing the five workers to die. The only way to avoid the deaths of these five workers is to hit a switch on your dashboard that will make the trolley go to the right, leading to the death of	106	6.2	4.3	3.3

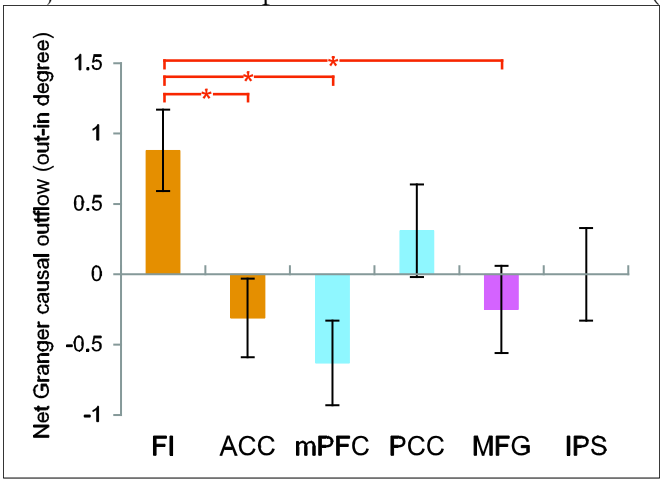
	the single worker. Would you hit the switch to avoid the deaths of the five workers?				
	You work for the government. Your group works to protect the environment. Today your group is voting about whether to adopt a new policy about toxic accidents. Both the old policy and the new policy you are considering have a risk of leading to people's deaths. The old policy has a 90% chance of leading to no deaths at all. However, it has a 10% chance of leading to 10,000 deaths. No one knows who these people will be. Under the new policy there will be 100 deaths, but no more. No one knows who these people will be. Would you vote to keep the old policy instead of changing to the new one?	114	6.9	2.3	2.3
	You are on the board of a charity in a poor country. The main river there floods every year. Each time this happens, 5,000 people who live downstream are left homeless. These floods do not affect people who live upstream. Some people in your charity want to build a dam to prevent these floods. This dam would cover a valley upstream with water. Villagers from nearby bring their cows to this valley to eat the grass. If this valley is covered with water, 1,000 of these villagers would have to move to find a new place to feed their cows. Would you vote against building the dam so these villagers can stay where they are?	115	6.4	4.3	3.0
	You work for the government. Your group works to protect the environment. Today your group is voting about whether to adopt a new policy about toxic accidents. Both the old policy and the new policy you are considering have a risk of leading to people's deaths. Under the old policy there will be 100 deaths, but no more. No one knows who these people will be. The new policy has a 90% chance of leading to no deaths at all. However, it has a 10% chance of leading to 500 deaths. No one knows who these people will be. Would you vote to keep the old policy instead of changing to the new one?	114	6.5	3.3	2.7
moral personal	You are the driver of a runaway trolley approaching a fork in the tracks. On the tracks going to the left are two railway workers. On the tracks going to the right is a single railway worker. If you do nothing, the trolley will go to the left, causing the two workers to die. The only way to avoid the deaths of these two workers is to hit a switch on your dashboard that will make the trolley go to the right, leading to the death of the single worker. Would you hit the switch to avoid the deaths of the two workers?	103	6.1	4.0	3.2
	A runaway trolley is heading down the tracks toward five workers, and will kill them if it keeps going. You are on a footbridge over the tracks, in between the approaching trolley and the five workers. Next to you on this footbridge is a stranger who is very large. The only way to save the lives of the five workers is to	109	6.6	3.0	3.2

	push this stranger off the bridge and onto the tracks below where his large body will stop the trolley. The stranger will die if you do this, but the five workers will be saved. Would you push the stranger onto the tracks to save the five workers?				
	You are part of a group of scientists living in a far away jungle. Rebels capture the whole group, including eight children. One rebel likes you, and tells you that his leader is going to kill all of you the next morning. He is willing to let you and the children escape, but as an act of friendship, he wants you to kill one of the other hostages, whom he dislikes. If you refuse his offer all of the hostages will die. If you accept, then the others will die in the morning, but you and the eight children will escape. Would you refuse to kill your fellow hostage despite the rebel's threats?	113	6.5	4.3	3.8
	You are on a cruise ship when a fire breaks out, forcing everyone to abandon ship. The lifeboats are carrying many more people than they should. The seas start to get rough, and your lifeboat begins to fill with water. If you do nothing, the boat will sink before help arrives and everyone on board will die. However, there is an injured person on board who will not survive even if help comes. If you throw that person overboard the boat will stay afloat and the rest of the passengers will be saved. Would you keep this injured person on the boat instead of throwing him overboard?	107	6.9	3.2	3.2
	You are leading a rescue team for seven miners that are stuck in an underground mine, which is flooding. Six miners are trapped at the bottom and will drown if not rescued soon. One miner is trapped higher in the elevator shaft and will not drown. The only way to rescue the six at the bottom is to quickly send down the mine elevator. If you do this, the one miner in the shaft will be crushed to death. If you do not send down the elevator, you will have enough time to rescue the one miner in the shaft. Would you send down the mine elevator to rescue the six miners at the bottom?	115	6.6	5.0	3.7
	You are leading a group that is lost in the wilderness. Your group includes a family of six with a genetic vitamin deficiency. A few people's kidneys contain large amounts of this vitamin. There is one such person in your group. The only way to save the lives of the six family members is to remove one of this man's kidneys and take the necessary vitamins from it. He will not die if you do this, but his health will get worse. He does not want to give his kidney, but you have the power to do what you choose. Would you allow this man to keep his kidney rather than save the vitamin-deficient family?	115	6.7	5.0	3.7
	You are negotiating with a powerful and determined terrorist. He is about to set off a bomb that will kill thousands of people. Your one advantage is that you have his teen-age son under your control. There is only one thing you can do to stop him from setting off his bomb. You can contact him over the video connection that he has created and break one of his son's	105	6.3	5.2	4.0

	arms. You can then threaten to break the other one if he does not give himself up. Would you break the boy's arm to keep the terrorist from killing thousands of people with his bomb?				
	An epidemic has spread worldwide killing millions of people. You have developed two substances in your underground shelter. One of them is a cure but the other one is deadly. You don't know which is which. Two people have run downstairs to your shelter trying to avoid the epidemic. The only way to identify the cure is to inject each of these people with one of the two substances. One person will live but the other will die. Then you will be able to start saving lives with the cure. Would you kill one of these people with a deadly injection to identify a cure that will save millions of lives?	111	6.2	3.7	3.3

Reading difficulty is measured by Flesch-Kincaid grade level as implemented in Microsoft Word 2003 (Microsoft Corp., Redmond, WA). Difficulty and emotion ratings reflect averages from a separate group of 6 healthy older control subjects.

Supplementary Figure 1. Net Granger causal outflow (out-in degree) of the right FI and ACC (SN), mPFC and PCC (DMN), and MFG and IPS (ECN) during the moral reasoning task in normal subjects. Asterisks represent differences at $P < 0.05$ (not corrected for multiple comparisons).



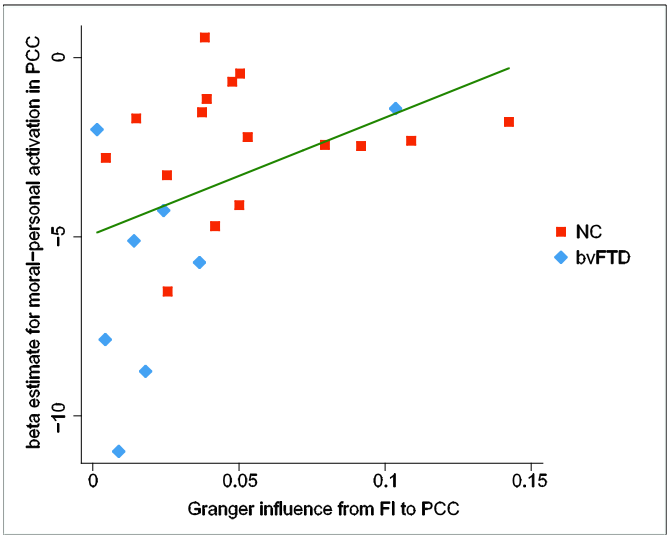
Supplementary Table 2A. Graph metrics for multivariate GCA in normal subjects.

	Out-degree	In-degree	Out-In degree
FI	2.25 ± 0.31	1.38 ± 0.26	0.88 ± 0.29
ACC	1.31 ± 0.26	1.63 ± 0.25	-0.31 ± 0.28
mPFC	0.69 ± 0.25	1.31 ± 0.25	-0.63 ± 0.30
PCC	1.50 ± 0.40	1.19 ± 0.20	0.31 ± 0.33
MFG	1.31 ± 0.21	1.56 ± 0.31	-0.25 ± 0.31
IPS	1.44 ± 0.28	1.44 ± 0.20	0.00 ± 0.33

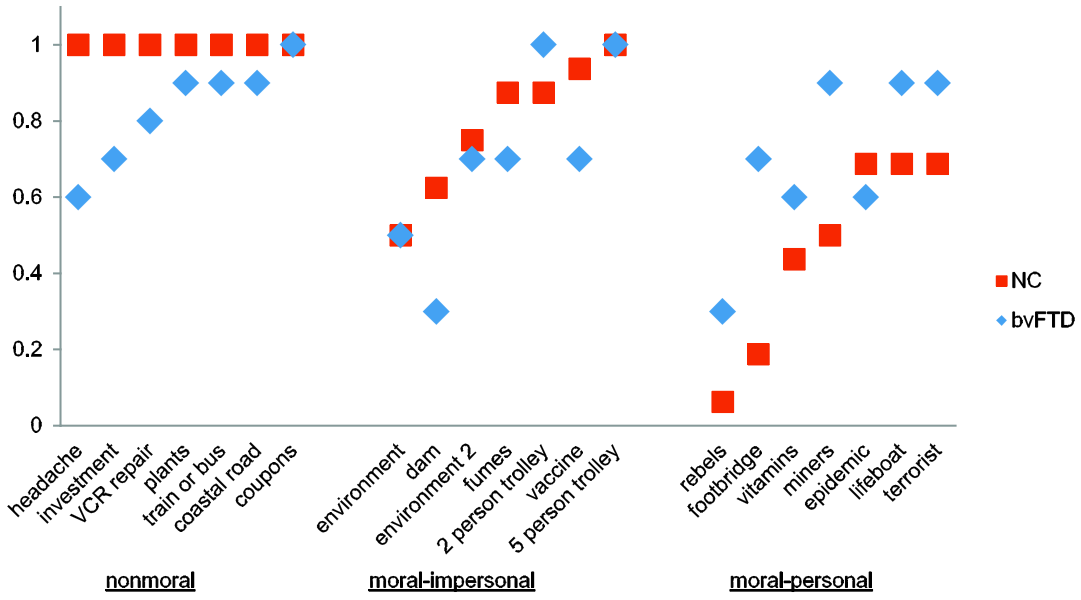
Supplementary Table 2B. Graph metrics for multivariate GCA in bvFTD patients.

	Out-degree	In-degree	Out-In degree
FI	1.25 ± 0.42	0.50 ± 0.18	0.75 ± 0.42
ACC	1.25 ± 0.34	1.50 ± 0.35	-0.25 ± 0.34
mPFC	0.75 ± 0.23	1.13 ± 0.28	-0.38 ± 0.35
PCC	0.50 ± 0.25	1.50 ± 0.31	-1.00 ± 0.35
MFG	1.50 ± 0.56	0.88 ± 0.21	0.63 ± 0.61
IPS	1.50 ± 0.47	1.25 ± 0.29	0.25 ± 0.42

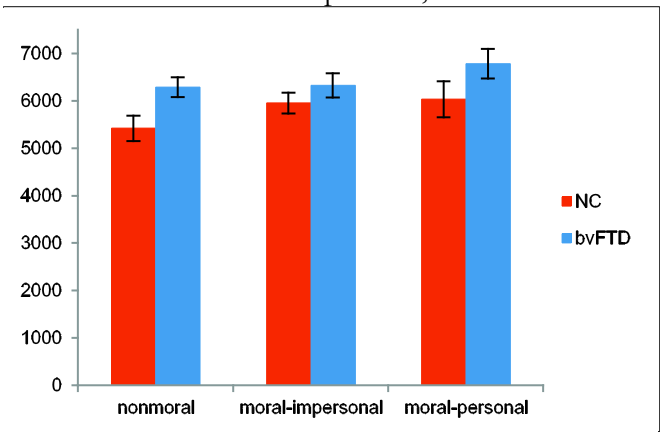
Supplementary Figure 2. Scatterplot of individual measures of Granger influence from the FI to PCC (bivariate analysis) and individual beta estimates for PCC activation during personal moral reasoning. Note that beta estimates are negative because the resting intertrial interval is treated as a baseline condition, though these values are more positive than those in the nonmoral comparison condition.



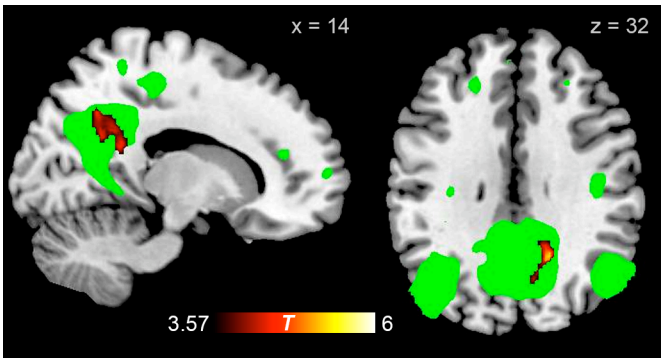
Supplementary Figure 3A. Proportion of utilitarian responses to each dilemma in controls and patients. Dilemmas within each category are arranged in ascending order of utilitarian responses among control subjects and secondarily ordered by utilitarian responses among FTD subjects.



Supplementary Figure 3B. Response times to nonmoral, moral-impersonal, and moral-personal dilemmas in controls and patients, in ms. Error bars refer to 1 standard error of the mean.



Supplementary Figure 4. Brain regions demonstrating greater activity for moral-personal dilemmas in controls than in bvFTD patients. x = 14. z = 32. For comparison, the default mode network as identified in resting state data from 15 control subjects is displayed in green at voxel-wise *P* = 0.0001.



Supplementary Table 3. Brain regions demonstrating greater activity for moral-personal dilemmas in controls than in bvFTD patients.

Region	x	y	z	Extent (mm3)	*P*	max *T*
Precuneus/posterior cingulate cortex	18	-54	34	4216	<0.001	5.75

P-values are corrected based on cluster extent, whereas max *T* is the *T* statistic of each local maximum.