

Fair play – Social norm compliance failures in behavioural variant frontotemporal dementia

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Abstract

Adherence to social norms is compromised in a variety of neuropsychiatric conditions. Functional neuroimaging studies have investigated social norm compliance in healthy individuals, leading to the identification of a network of fronto-subcortical regions that underpins this ability. However, there is a lack of corroborative evidence from human lesion models investigating the structural anatomy of norm compliance across this fronto-subcortical network. To address this, we developed a neuroeconomic task to investigate social norm compliance in a neurodegenerative lesion model: behavioural variant frontotemporal dementia, a condition characterised by gross social dysfunction. The task assessed norm compliance across three behaviours that are well studied in the neuroeconomics literature: fairness, prosocial and punishing behaviours. We administered our novel version of the Ultimatum Game in 22 behavioural variant frontotemporal dementia patients and 22 age-matched controls, to assess how decision-making behaviour was modulated in response to 1) fairness of monetary offers, and 2) social context of monetary offers designed to produce either prosocial or punishing behaviours. Voxel-based morphometry was used to characterise patterns of grey matter atrophy associated with task performance. Acceptance rates between patients and controls were equivalent when only fairness was manipulated. However, patients were impaired in modulating their decisions in response to social contextual information. Patients' performance in the punishment condition was consistent with a reduced tendency to engage in punishment – this was associated with decreased grey matter volume in the anterior cingulate, orbitofrontal cortex, left dorsolateral prefrontal cortex and right inferior frontal gyrus. In the prosocial condition, patients' performance suggested a reduced expression of prosocial behaviour, associated with decreased grey matter in the anterior insula, lateral orbitofrontal cortex, anterior cingulate and dorsal striatum. Acceptance rates in the Ultimatum Game were also significantly related to

impairments in the everyday expression of empathic concern. In conclusion, we demonstrate that compliance to basic social norms (fairness) can be maintained in behavioural variant frontotemporal dementia, however more complex normative behaviours (prosociality, punishment) that require integration of social contextual information are disrupted in association with atrophy in key fronto-striatal regions. These results suggest that the integration of social contextual information to guide normative behaviour is uniquely impaired in behavioural variant frontotemporal dementia, and may explain other common features of the condition including gullibility and impaired empathy. Our findings also converge with previous functional neuroimaging investigations in healthy individuals and provide the first description of the structural anatomy of social norm compliance in a neurodegenerative lesion model.

Key words: Social norm compliance; Fairness; Prosocial; Punishment; Empathy; Behavioural variant frontotemporal dementia

Introduction

Decisions in social contexts are complex and often require compromise between self-interest and consideration of others. Ever implicit in such decision-making is a regard for social norms – that collective sentiment of what constitutes appropriate behaviour, which is so fundamental to adaptive human interaction (Buckholtz and Marois, 2012). Despite recent advances (Spitzer *et al.*, 2007, Baumgartner *et al.*, 2011, Ruff *et al.*, 2013), very little is known regarding the neurobiology of social norm compliance. Even more pressing is the need for a framework to account for dysfunctional social norm compliance, which underscores symptoms across a range of neuropsychiatric conditions.

Certain social normative behaviours are increasingly studied in the neuroeconomics literature. These include the tendency to engage in prosocial behaviours such as fairness or altruism, and the tendency to enact punishment upon others who violate social norms (Buckholtz and Marois, 2012). Despite the diversity of social norms at play, insights from the field of neuroeconomics implicate a distinct network of fronto-striatal-insular regions that appears to mediate compliance to social norms (Sanfey *et al.*, 2003, Spitzer *et al.*, 2007, Baumgartner *et al.*, 2011, Chang and Sanfey, 2013, Ruff *et al.*, 2013, Gabay *et al.*, 2014, Ruff and Fehr, 2014).

The behavioural variant of frontotemporal dementia (bvFTD), a neurodegenerative condition with insidious, progressive change in personality and social interactions, represents the prototypical example of disordered social norm compliance. Patients commonly exhibit behavioural changes considered under this rubric, including loss of empathy and insight, disinhibited remarks or behaviour, egocentricity, impulsive spending or gambling, and gullibility (Piguet *et al.*, 2011). Intriguingly, the earliest sites of pathology overlap with those

regions implicated in social norm compliance, most notably in the ventromedial prefrontal cortex, anterior cingulate, insula, amygdalae and striatum (Broe *et al.*, 2003, Seeley *et al.*, 2008, O'Callaghan *et al.*, 2014, Bertoux *et al.*, 2015). Decision-making paradigms traditionally used in the literature, which typically involve monetary gambles under conditions of risk and ambiguity, are found to have limited utility in bvFTD (Gleichgerrcht *et al.*, 2010, Bertoux *et al.*, 2013, Kloeters *et al.*, 2013). Convergent approaches incorporating measures of social processing and decision-making represent a promising avenue to better detect the complex social-contextual deficits that typify bvFTD (Ibañez and Manes, 2012).

The Ultimatum Game, a paradigm drawn from the neuroeconomics literature, offers a means of gauging normative decision-making behaviours in a social context. The task requires participants to either accept or reject monetary offers, varying in their degree of 'fairness'. A consistent observation is that healthy participants frequently reject unfair offers, in order to punish their opponent, even though this decision incurs a personal cost (Güth *et al.*, 1982, Sanfey *et al.*, 2014). Such unfair offers are considered a violation of 'fairness norms' and therefore deserve sanctioning (Fehr and Fischbacher, 2004).

Here, we sought to investigate social normative behaviour in bvFTD by introducing social contextual factors in the Ultimatum Game. In this novel manipulation, we included 'social framing' conditions intended to either induce participants to accept more offers due to compassion/desire to help (prosocial), or to incite the desire to punish via rejecting more offers (punishing). Fairness behaviour has deep developmental roots (Fehr *et al.*, 2008, Castelli *et al.*, 2014), and examples of altered responses to fairness on the Ultimatum Game have been attributed to states of exaggerated emotional reactivity (Koenigs and Tranel, 2007, Crockett *et al.*, 2008) which is not present in bvFTD. Because of this, we predicted that

fairness behaviours may remain robust in bvFTD and that patients would demonstrate intact expression of fairness and thus perform similarly to healthy controls in the classic Ultimatum Game. However, in contrast, we predicted patients would have difficulty adapting their behaviour to engage in prosocial or punishing choice in the social framing conditions, as they require the integration of social contextual factors, an ability specifically known to be disrupted in bvFTD (Ibañez and Manes, 2012). We anticipated that patients' abnormal expression of social norms in the social framing conditions would correlate with grey matter loss in discrete regions within the fronto-subcortical network previously implicated in social norm compliance.

Materials and methods

Case selection

Twenty-two bvFTD patients were recruited from the FRONTIER dementia clinic, at Neuroscience Research Australia. All patients met current consensus criteria for bvFTD (Neary *et al.*, 1998, Rascovsky *et al.*, 2011). Twenty-two age- and education-matched healthy controls were selected from a volunteer panel. The Mini-Mental Status Examination (MMSE) was administered as a measure of general cognition. The Frontotemporal Dementia Rating Scale (FRS; (Mioshi *et al.*, 2010)) was used as a measure of clinical staging for the patients. In brief, the FRS is an informant-rated staging scheme validated for use in bvFTD, tapping into a variety of behavioural and functional symptoms. Lower percentage scores on the FRS indicate more severe impairment, with six stages ranging from *very mild* to *profound*. The study was approved by the local Ethics Committees and all participants provided informed consent in accordance with the Declaration of Helsinki. See Table 1 for demographic details and clinical characteristics.

Background Neuropsychology

General neuropsychological tests to assess executive function and memory were administered to both patients and controls. Executive function measures included attention and working memory assessed via the digit span task (total score of digits repeated forwards and backwards; (Wechsler, 1997)). To assess psychomotor speed and attentional set-shifting, the Trail Making Test, parts A and B, were administered (Spreen, 1998). Verbal memory encoding and retrieval were assessed using the Rey Auditory Verbal Learning Test (RAVLT; (Lezak, 2004), sum of trials 1-5 and the delay score, respectively. Copying and short-term visual recall were assessed using the Rey Osterrieth Complex Figure (Meyers, 1995).

Capacity for Empathy

The Cambridge Behavioural Inventory-Revised (CBI-R; (Wear *et al.*, 2008) was used to assess behavioural disturbance in the patients. The CBI-R is a 45 item informant-rated questionnaire probing a variety of neuropsychiatric, cognitive and functional symptoms, rating their frequency of occurrence from 0 (*never*) to 4 (*constantly*). As such, higher CBI-R scores indicate greater behavioural dysfunction. To specifically assess empathy, we extracted scores from the item that best exemplifies deficits in this ability: “Appears indifferent to the worries and concerns of family members”. Importantly, this question addresses empathic concern – an aspect of empathy primarily affected in bvFTD (Baez *et al.*, 2014).

Ultimatum Game

We created a modified Ultimatum Game with baseline and reappraisal versions, using the same monetary amounts and fair to unfair offer ratios that have been previously described (Koenigs and Tranel, 2007). In both the baseline and reappraisal versions, participants acted in response to different proposers who offered to split a hypothetical \$10 with them. The

proposer - responder offers ranged from fair (\$5 - \$5; \$6 - \$4), to unfair (\$7 - \$3; \$8 - \$2; \$9 - \$1). Based on previous findings (Güth *et al.*, 1982), including those validated in neurological patients and in older adults (Koenigs and Tranel, 2007), we operationalised 'fair' acceptance rates as the average of \$5 - \$5 or \$6 - \$4, and the 'unfair' as the average of \$7 - \$3, \$8 - \$2 and \$9 - \$1 acceptance rates.

In the baseline condition, participants were informed they would play against 22 different people, each of whom had been given \$10 to divide. It was explained that proposers were free to decide how to split the money, but participants could choose whether to accept the offer (resulting in a payout for both players) or reject the offer (resulting in \$0 for both). An example of baseline trials is shown in Figure 1 (a). In each trial a black and white photograph of a neutral face, with the caption "[name] has made you an offer" was presented on a computer screen for 3.5 seconds. This was followed by a decision screen where the offer was stated, e.g., "[name] gets \$7, you get \$3", and a prompt to either "accept" or "reject". This decision screen was displayed until a response was made, followed by a feedback screen of "you get \$3" or "you both get \$0" (4 seconds) depending on the response made.

In the social framing version, participants were informed they would play against a set of 22 new people, each given \$10 to divide, with the same contingences applying for accepting or rejecting offers. However, now they were provided information about the proposers' current circumstances. The prosocial condition framed proposers as poor, or 'down on their luck', and was designed elicit a higher acceptance rate on the basis that participants should feel sorry for the proposer. The punishing condition framed proposers as rich to encourage higher rejection rates or punishing behaviour, as the offers (particularly the unfair ones) should evoke a heightened sense of unfairness. Social framing trials are exemplified in Figure 1, (b)

and (c). As in the baseline condition, in each trial a black and white photograph of a neutral face was presented, followed by a description screen (4.5 seconds). Descriptions were restricted to brief and uncomplicated language. Examples of the prosocial condition included “[name] lost his/her house in a fire”, “[name] is saving for his/her son's operation”, “[name] is homeless” and examples of the punishing condition included “[name] owns an international company”, “[name] just won the lottery”, “[name] is a wealthy investment banker”. A decision screen with the offer followed, then a feedback screen. To ensure patients understood the terminology (i.e., that winning the lottery or being a wealthy investment banker would be associated with being rich; or being homeless would be associated with being poor etc.), a checklist was administered at the end of the experiment. All patients included in the study demonstrated intact understanding of the social framing terminology.

In both the baseline and social framing conditions the 22 trials comprised two of each fair offer and six of each unfair offer. To control for possible gender biases deriving from the stimulus set, within each condition half of the presented faces were female and half male. In addition, the offer amounts were paired with proposers on a random cycle, to control for the possibility that features of a proposer (for example, physical attractiveness) might induce systematic response biases. The photos were of neutral expressions across all conditions, to further reduce the possibility of eliciting response biases on the basis on perceived friendliness/unfriendliness. For the social framing condition, an equal mix of prosocial and punishing descriptors made up the 22 trials, and these were presented in a randomised order. Each participant completed the baseline version first, followed by the social framing version. Participants were not awarded actual monetary payouts in relation to the task and were not

compensated for their participation; they were, however, instructed to make their choices on the basis of how they would act in a real-life situation.

For the Ultimatum Game, the outcome measures were percentage acceptance rates for fair and unfair offers in each of the conditions. Further to this, we created percentage scores to reflect 'change from baseline' in the social framing conditions, in order to see both the extent and direction that acceptance rates deviated from baseline in response to the social framing information. The extent of each participants 'change from baseline' scores were calculated by subtracting acceptance rates in the prosocial/punishing conditions from baseline acceptance rates, then taking the reciprocal of this to represent directionality of the change. These change scores were calculated separately for fair and unfair offers.

Behavioural analysis

Demographics and background neuropsychology variables were analysed by two-tailed independent samples *t*-tests, using SPSS v. 22 (Chicago, IL, USA). For the Ultimatum Game, we analysed our results by estimating a logistic GEE (generalised estimating equations) model with an exchangeable working correlation structure, which accounts for within-subjects correlation across decisions. We did not use a repeated-measures ANOVA analysis on proportions (i.e., rejection rates) for two reasons: the ANOVA assumption of variance homogeneity is violated for categorical data, and ANOVA does not respect the upper and lower bounds of 0 and 1 for proportions (see (Jaeger, 2008) for a more complete exposition of arguments favouring a logit specification over ANOVA for categorical variables). The binary dependent variable is the decision to accept or reject an offer, and the independent variables are a three-way factorial of the fairness level (fair vs. unfair acceptance rates), group membership (control vs. bvFTD) and the social framing condition (baseline vs.

punishing vs. prosocial), as well as a set of control variables. Variables were introduced in the main analysis to control for the effects of gender, given previous evidence of gender effects in the Ultimatum game (Croson and Gneezy, 2009), and also to control for the impact of patients' cognitive deficits on Ultimatum Game performance. We controlled for gender by including a main effect of gender, and two-way interactions of gender with condition, fairness, and group. We controlled for cognitive ability using neuropsychological variables covering three cognitive domains (i.e., episodic memory as measured by the RAVLT delay score; speeded set-shifting as indexed by the TMT-B; attention/working memory as assessed by Digit Span total). Consequently, all of the results presented in the main text have been controlled for the possible effects of these variables. All results marked as "post-hoc comparisons" are corrected for multiple comparisons using the Sidak correction. Note, 95% confidence intervals of effects will be presented throughout in [...]. GEE analyses were conducted using the Stata 13 software package (Stata Corporation, College Station, Tx).

Imaging acquisition

Whole-brain T1 images were acquired using 3T Philips MRI scanners with standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 x 256, 200 slices, 1 x 1 mm² in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms.

Voxel-based morphometry (VBM) analysis

3D T1-weighted sequences were analysed with FSL-VBM, a voxel-based morphometry analysis (Ashburner and Friston, 2000, Good *et al.*, 2001), part of the FSL software package <http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html> (Smith *et al.*, 2004). First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang

et al., 2001) from brain extracted images. The resulting grey matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MNI152) using the nonlinear registration approach (FNIRT (Andersson *et al.*, 2007a, Andersson *et al.*, 2007b)), which uses a b-spline representation of the registration warp field (Rueckert *et al.*, 1999). Registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (full width half maximum = 8 mm). On the basis of previous studies that defined neural correlates of the Ultimatum Game (Sanfey *et al.*, 2003) and social norm processing (Spitzer *et al.*, 2007) across various prefrontal, striatal and limbic regions, we created a region-of-interest (ROI) mask using the Harvard-Oxford cortical and subcortical structural atlases. The following bilateral atlas regions were included in the mask: frontal pole, frontal orbital cortex, subcallosal cortex, frontal medial cortex, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, cingulate gyrus (anterior division), paracingulate gyrus, caudate, putamen, nucleus accumbens, insula cortex and amygdala.

Group differences in grey matter intensity between patients and controls, within the fronto-subcortical mask, were compared using a voxelwise general linear model (GLM). Significant clusters were formed by employing the threshold-free cluster enhancement (TFCE) method (Smith and Nichols, 2009). The TFCE method is a cluster-based thresholding method which does not require the setting of an arbitrary cluster forming threshold (e.g., t, z). Instead, it takes a raw statistics image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The TFCE image is then turned into voxel-wise p-values via permutation testing. We employed a permutation-based non-parametric testing with 5000 permutations (Nichols and Holmes, 2002). Differences in grey

matter intensity between patients and controls were assessed via *t*-tests, tested for significance at $p < .05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space.

Following this, correlations between Ultimatum Game performance and grey matter intensity were conducted. Both patients and controls were included in the analysis, to add greater variance in the behavioural scores thereby increasing the study's statistical power to detect brain-behaviour relationships (Sollberger *et al.*, 2009, Irish *et al.*, 2014). The 'change from baseline' scores for unfair offers in both the positive and negative social framing conditions were entered as covariates in separate GLM matrices. For additional statistical power, a covariate only statistical model with either a positive or negative *t*-contrast was used. These contrasts were applied to test the association between the degree of patients' abnormal behavioural performance in the social framing condition (i.e., if acceptance rates were lower in the prosocial condition or higher in the punishing condition) and grey matter loss. Therefore, a positive *t*-contrast was applied to 'change from baseline' in the prosocial condition, in order to index an association between decreasing grey matter volume and extent of lowered acceptance rates. A negative *t*-contrast was applied to 'change from baseline' scores in the punishing condition, which indexed an association between decreasing grey matter volume and the extent of higher acceptance rates. Positive and negative contrasts were tested with 5000 permutations and reported at a significance level of $p < .001$ uncorrected and at a cluster threshold of greater than 35 contiguous voxels.

Results

Demographics and background neuropsychology

As shown in Table 1, patients and controls were **not significantly different** for age and education levels (t values $-.02$ and 2.0 , p values $.985$ and $.061$). Patients had significantly lower MMSE scores ($t = 6.1$, $p < .001$). In terms of background neuropsychology, patients had significantly slower psychomotor speed on TMT-A ($t = -2.2$, $p < .05$). Patients also had worse working memory/attention, speeded set-shifting and visuospatial copying (digit span: $t = 5.6$, $p < .001$; TMT-B: $t = -4.9$, $p < .001$; RCF copy: $t = 3.7$, $p < .01$). Patients' scores were significantly reduced across verbal and non-verbal memory encoding and retrieval (RAVLT 1-5: $t = 6.5$, $p < .001$; RAVLT delay: $t = 5.5$, $p < .001$; RCF 3 minute delay: $t = 3.2$, $p < .01$).

Ultimatum Game baseline condition

Acceptance rates in the baseline condition are shown in Figure 2. The group by fairness level interaction was not significant ($\chi^2(1) = 0.03$, $p = 0.870$). The main effect of group was not significant ($\chi^2(1) = 0.69$, $p = 0.405$), but there was a significant main effect for fairness level ($\chi^2(1) = 53.83$, $p < 0.0001$). The acceptance rates for both controls and bvFTD patients fell significantly in the unfair condition compared to the fair condition by 35.5% [19.6%-51.4%] and 37.4% [23.1%-51.7%], respectively. The absence of a significant interaction between fairness and group implies that the acceptance rates of the two groups were not significantly different within both the fair and unfair condition. Consequently, both patients and controls exhibited a normative response to the fairness manipulation, that is, accepting significantly fewer unfair offers. See Supplementary Figure 1, panel a) for a graphical representation of acceptance rates at each fairness level.

Social framing conditions

This section compares acceptance rates across the two social framing conditions (punishing vs. prosocial), as illustrated in Figure 3. The overall three-way interaction of fairness level,

social framing and group was not significant ($\chi^2(1)=2.63, p=0.105$). The fairness by group interaction was not significant ($\chi^2(1)=0.99, p=0.319$), indicating that response rates in both controls and patients were modulated to a similar degree by fairness level – a similar pattern to that seen in the baseline condition. By contrast, social framing interacted with fairness ($\chi^2(1)=12.96, p<0.001$). More importantly, there was also a significant social framing by group interaction ($\chi^2(1)=8.75, p<0.01$), such that the social framing condition modulated the responses of both groups differentially.

For the social framing by fairness interaction, post-hoc comparisons revealed that for unfair offers the increase in the acceptance rate comparing the punishing to the prosocial conditions, 29.3% points [21.1%-37.5%], was significant ($\chi^2(1)=64.05, p<0.0001$). However, acceptance rates for fair offers were not significantly different across the punishing and prosocial conditions ($\chi^2(1)=2.80, p=0.179$).

Regarding the social framing by group interaction, post-hoc comparisons showed that in the punishing condition, acceptance rates for controls and patients were not significantly different ($\chi^2(1)=0.14, p=0.916$). However, in the prosocial condition patients accepted significantly less offers than controls ($\chi^2(1)=13.72, p<0.001$). Controls demonstrated significantly lower acceptance rates (a difference of 37.2% [23.5%-50.1%]) in the punishing versus prosocial condition ($\chi^2(1)=37.09, p<0.0001$). Patient acceptance rates were also significantly lower in the punishing versus prosocial conditions, 14.9% difference [7.3%-22.5%] ($\chi^2(1)=19.32, p<0.0001$). Importantly, the effect size of the change in patients' acceptance rates (across conditions) is significantly less than that of the controls 22.2% [7.5%-37.0%] ($\chi^2(1)=8.75, p<0.01$). Hence, patients were significantly less influenced by condition than controls

indicating a muted response to the prosocial framing. (See Supplementary Figure 1, panels b) and c) for acceptance rates at each offer level of the social framing conditions).

Comparisons with the baseline condition

Comparisons with baseline are shown in Figure 4. The overall three-way interaction of fairness level, social framing and group was not significant ($\chi^2(2)=3.37, p=0.186$). The fairness by group interaction was not significant ($\chi^2(1)=0.45, p=0.5$), indicating that acceptance rate changes from the baseline in both controls and patients were modulated to a similar degree by fairness level. By contrast, social framing interacted with fairness ($\chi^2(2)=26.15, p<0.001$). Also, there was a significant social framing by group interaction ($\chi^2(2)=9.34, p<0.01$), indicating that the social framing condition modulated the change in acceptance rates from the baseline for both groups differentially.

Post-hoc comparisons revealed the following findings. For fair offers, in both the prosocial or punishing conditions neither control nor patient acceptance rates differed significantly from baseline (p -values ranging from 0.93 to 1.00) (see Figure 4, panel a). For unfair offers in the punishing condition, patients accepted on average 11% more than their baseline levels, although this difference was not significant ($\chi^2(1)=2.33, p=0.663$). This contrasts with the control group whose acceptance rates for unfair offers in the punishing condition were virtually identical to the baseline rates, a difference of only 0.06% ($\chi^2(1)=0.00, p=1.00$) (See Figure 4, panel b). For unfair offers in the prosocial condition, patients' acceptance rates were significantly higher than their baseline levels by 28.5% ($\chi^2(1)=15.57, p<0.001$). Controls' unfair acceptance rates were also significantly higher than their baseline levels by 43.1% ($\chi^2(1)=44.99, p<0.0001$) (See Figure 4, panel b). For the unfair condition, we compared the difference between acceptance rates in the punishing condition versus

acceptance rates in the prosocial condition. Both groups accepted significantly more offers in the prosocial condition, compared to the punishing condition, with controls accepting 43% more [27.0%-59.0%] ($\chi^2(1)=36.26, p<0.0001$), but patients accepting only 17.1% more [8.1%-26.0%] ($\chi^2(1)=18.43, p<0.0001$). The magnitude of this change differed significantly between the groups (difference: 25.9% [8.8%-43.0%] ($\chi^2(1)=8.81, p<0.01$)), consistent with the patients displaying a divergent response to social framing, characterised by a tendency for higher acceptance rates in the punishing condition and a muted response to the prosocial condition.

Relationship to empathy

To investigate the effect of empathy on acceptance rates in the patients, we estimated a GEE logistic model using a three-way factorial design of the fairness level, social framing condition and the level of empathy impairment (minimal vs. severe). We categorised patients on the basis of their score on the CBI-R empathy item (ranging from 0 to 4, higher scores indicating more significant impairment). Minimal impairment was defined as values ranging from 0-3 and severe impairment as values of 4. A total of nine patients were in the minimally impaired range (three patients were rated 0, one patient scored 1, two patients had a score of 2, and three had a score of 3), the remaining thirteen patients were in the severely impaired range, with scores of 4. The three-way interaction between empathy, fairness, and social framing condition was not significant ($\chi^2(1)=0.78, p=0.377$). We found significant main effects of empathy ($\chi^2(1)=5.03, p<0.05$), fairness ($\chi^2(1)=22.89, p<0.001$) and social framing ($\chi^2(1)=9.88, p<0.01$). Two-way interactions between empathy and social framing, and fairness and social framing, were not significant ($\chi^2(1)=1.21, p=0.271$ and $\chi^2(1)=0.75, p=0.377$, respectively). However, we found a significant interaction between empathy and fairness ($\chi^2(1)=4.83, p<0.05$).

Post-hoc comparisons within the significant empathy and fairness interaction revealed that for unfair offers, those with severely impaired empathy had significantly lower acceptance rates than those with minimal impairment (39.0% vs. 61.3% accepted; $\chi^2(1)=6.46$, $p<0.05$). However, no difference was found between severely impaired and minimally impaired subjects for fair offers (82.2% vs. 74.4% accepted; $\chi^2(1)=0.52$, $p=0.718$). Together indicating that reduced empathy was specifically associated with lower acceptance rates for unfair offers.

Ultimatum Game – control variables

Here we report analysis of the gender and cognitive control variables that were included in the main analysis. For the individual cognitive variables, no effect of TMT-B or RAVLT delay was found on acceptance rates (coeff.=0.002, $z=0.10$, $p=0.918$ and coeff.=−0.026, $z=−0.77$, $p=0.442$ respectively), however there was a significant main effect for digit span total (coeff.=0.173, $z=3.45$, $p<0.01$), indicating that the higher the digit span of a subject, the higher their acceptance rate across conditions. The main effect of gender was significant ($\chi^2(1)=5.93$, $p<0.05$), as was the interaction with fairness ($\chi^2(1)=5.16$, $p<0.05$). Post-hoc comparisons reveal that for unfair offers males had significantly higher acceptance rates, 62.6%, than females 45.7% ($\chi^2(1)=6.99$, $p<0.05$). No significant difference was found in acceptance rates for fair offers ($\chi^2(1)=0.06$, $p=0.805$). The interactions of gender with condition and group were not statistically significant ($\chi^2(2)=2.66$, $p=0.265$ and $\chi^2(1)=1.13$, $p=0.289$, respectively). The lack of significant interaction between gender and condition suggests that a gender effect is unlikely to account for specific deficits on the social aspect of the tasks exhibited by bvFTD patients. However, future studies with equal gender distributions will be important to explore potential within-group variations in performance on the Ultimatum Game in bvFTD.

VBM analysis – Atrophy pattern in bvFTD group

The bvFTD group was initially contrasted with controls to reveal overall patterns of grey matter intensity decrease in the fronto-subcortical mask. Patients showed characteristic patterns of atrophy throughout the fronto-subcortical regions of interest. For details, see Supplementary Table 1 and Supplementary Figure 2.

VBM analysis – Ultimatum Game

Regions of decreased grey matter intensity associated with higher acceptance rates for unfair offers in the punishing condition are shown in Table 2, section a) and Figure 5, panel a). These regions included the left dorsolateral prefrontal cortex, right inferior frontal gyrus, anterior cingulate and paracingulate cortices and medial orbitofrontal cortex and subgenual cingulate. The regions of decreased grey matter intensity associated with lower acceptance rates in the prosocial condition are shown in Table 2, section b) and Figure 5, panel b). These regions included a large cluster encompassing the left dorsal putamen and left anterior insular, other regions included the right dorsal posterior putamen and caudate body, also the left lateral orbitofrontal cortex. (See Supplementary Table 2 for reports of within group correlations between grey matter intensity and behavioural scores).

Discussion

We present a novel neuroeconomic task to investigate normative social decision-making behaviour in a neurodegenerative lesion model characterised by gross social dysfunction (bvFTD). For the first time, we describe the decision-making behaviour in bvFTD across three social normative scenarios: fairness, punishment and prosocial. Behaviourally, we demonstrate intact responses to fairness in the patients. In contrast, they show muted

expression of punishing and prosocial behaviour, associated with discrete regions of fronto-striatal atrophy. Our findings suggest that whilst expression of basic normative behaviour may remain intact in bvFTD, more complex normative behaviours that rely on the integration of social contextual information are compromised.

Equivalent responses to fairness between patients and controls may, at first glance, seem difficult to reconcile, considering that core emotion processing regions known to underpin fairness behaviour are compromised in bvFTD. Previous investigations in ventromedial prefrontal cortex lesion patients, or during dietary serotonin depletion, indicate that emotion regulatory mechanisms interact with perceptions of unfairness. Accordingly, exaggerated emotional reactions lead to elevated rejection rates (Koenigs and Tranel, 2007, Crockett *et al.*, 2008, Shamay-Tsoory *et al.*, 2012, Crockett *et al.*, 2013). In contrast, the well-described blunting of emotional reactivity in bvFTD (Sturm *et al.*, 2006) can explain why we do not see those same elevated rejection rates as patients with discrete prefrontal lesions, who often manifest exaggerated anger and irritability in frustrating situations (Koenigs and Tranel, 2007). An interaction between emotional blunting and fairness behaviour has not been established in the literature. Our findings raise the possibility that fairness behaviour may not be similarly moderated by reduced emotional reactivity as it is by exaggerated emotional states. This supports that conclusion that perception of fairness is a dissociable construct from emotional state, and that it is maintained in bvFTD.

In contrast, patients differed from controls in terms of their engagement in either punishing or prosocial behaviour. These deviations from normative behaviour were associated with specific regions of fronto-striatal grey matter atrophy. In the punishing condition (i.e., framing proposers as rich to provoke an increased sense of unfairness, and encourage higher

rejection rates), bvFTD patients showed a different pattern to controls, by a tendency to accept more than their baseline levels. This contrasted with controls' acceptance rates, which were more in keeping with their baseline levels – suggesting that controls' responses were not modulated by information framing proposers as rich. The extent that patients' acceptance rates were elevated relative to their baseline levels was correlated with atrophy particularly in ventromedial prefrontal cortex regions (medial orbitofrontal/subgenual cortex, mid/anterior cingulate) but also in the right inferior frontal gyrus and left dorsolateral prefrontal cortex.

Although the punishing condition did not induce punishment behaviour in controls, bvFTD patients' tendency to accept more in this condition suggests a potential 'misuse' of social contextual information, whereby potentially negative social contextual information is not exploited to guide economic decisions. Such a finding is consistent with the commonly noticed financial gullibility of bvFTD patients. Maladaptive financial decision making in bvFTD is pervasive in both everyday life and experimental contexts (Manes *et al.*, 2010, Manes *et al.*, 2011, Perry *et al.*, 2013, Chiong *et al.*, 2014). Extravagant spending, economic negligence and financial vulnerability can emerge long before a bvFTD diagnosis is achieved. A potentially compromised ability to integrate negative social cues with economic decisions warrants further investigation in bvFTD, as it may emerge as a critical area for early diagnostic assessment.

Our imaging findings for the punishing condition reveal a putative neural network that could underpin patients' inability to effectively employ negative social contextual information. The extent to which patients were less likely to engage in punishing behaviour was mediated by atrophy in regions at the intersection of emotion- and value-based social decision-making, namely the ventromedial prefrontal cortex and mid/anterior cingulate. This is consistent with

the involvement of these regions in evaluating both reward and punishment, and integrating value with social and emotional information to inform subsequent behaviour (Rushworth *et al.*, 2007, Etkin *et al.*, 2011, Apps *et al.*, 2013). The dorsomedial prefrontal cortex, in particular, emerges as an important integrative hub for social behaviour, given its role in person perception and mentalising (Amodio and Frith, 2006).

We also show that the right inferior frontal gyrus, and left dorsolateral prefrontal cortex atrophy related to a reduced tendency to engage in punishing behaviour. Bilateral dorsolateral prefrontal cortex activation has been implicated in social norm compliance (Spitzer *et al.*, 2007), and non-invasive brain stimulation to disrupt the right dorsolateral prefrontal cortex alters social norm compliance in economic decision-making (Knoch *et al.*, 2006, Ruff *et al.*, 2013). One study using the Ultimatum Game demonstrated a significant decline in rejection rates of unfair offers after transcranial magnetic stimulation to the right dorsolateral prefrontal cortex, which induced decreased activity of the right dorsolateral prefrontal cortex and posterior ventromedial cortex, and connectivity between them (Baumgartner *et al.*, 2011). Our results corroborate that combined ventromedial and dorsolateral prefrontal cortex atrophy is associated with an unwillingness to engage in punishing behaviour. In the context of the Ultimatum Game, rejecting unfair offers entails a more immediate inhibition of self-interest, as monetary gain is foregone in order to penalise the proposer's violation of the fairness norm. The dorsolateral prefrontal cortex has been linked to the ability to override self-interest via functional imaging and electrical stimulation studies (Rilling and Sanfey, 2011), using a structural lesion model we highlight that the right inferior frontal gyrus may be a critical locus involved in this process. The right inferior frontal gyrus is implicated in various forms of inhibitory control (Aron, 2011). Inhibitory dysfunction is well described in bvFTD (O'Callaghan *et al.*, 2013a) and has been linked to orbitofrontal and inferior frontal

cortex abnormalities (Peters *et al.*, 2006, Hornberger *et al.*, 2011, O'Callaghan *et al.*, 2013b, Hughes *et al.*, 2015). Together, the structural neural correlates we describe here converge across circuitry involved in inhibition and emotion/reward processing, confirming a role for this network in mediating alterations to normative social function in bvFTD.

In terms of the prosocial condition (i.e., to frame proposers as being 'in need' to encourage higher acceptance rates), patients showed a tendency toward prosocial behaviour, albeit to a lesser extent than controls. The extent to which patients deviated from normative responses in this condition, by accepting less than their baseline levels, was associated with atrophy in dorsal striatal regions, left anterior insula and left lateral orbitofrontal cortex. A proximate mechanism for prosocial behaviour is thought to be the subjective reward derived from helping another (Fehr and Fischbacher, 2003). In line with our finding that dorsal striatum atrophy mediated the muted prosocial response, functional activation studies implicate the striatum in social reward processing (Fehr and Camerer, 2007, Bhanji and Delgado, 2014), although the exact subdivisions associated with social rewards have not been established. Currently, both dorsal and ventral striatum have been linked to social reward valuation and learning, vicarious social reward, and signalling reward inequality (Báez-Mendoza and Schultz, 2013). However, convergent evidence from non-social paradigms implicates the dorsal striatum in signalling reward- and motivation-based information that drives subsequent action selection (O'Doherty, 2004, O'Doherty *et al.*, 2004, Balleine *et al.*, 2007). Taken together, the dorsal striatum may play a unique role in computing social reward and biasing action-output geared to seek rewarding social interactions.

Activation in the anterior insula has consistently been linked with Ultimatum Game performance in healthy people (Sanfey *et al.*, 2003, Tabibnia *et al.*, 2008, Civai *et al.*, 2012,

Corradi-Dell'Acqua *et al.*, 2013). A strong association between the anterior insula and negative emotional states (Damasio *et al.*, 2000) was taken as evidence that this region mediated the negative emotional reactions that led to rejecting unfair offers. However, an alternative interpretation is that the insula has a broader role in both detecting inequality and motivating decisions to restore inequality (Rilling and Sanfey, 2011, Gabay *et al.*, 2014). Our findings show that anterior insula damage may not necessarily affect normative responses to fairness, but that it is related to a reduced expression of prosocial behaviour, consistent with its hypothesised broader role. In keeping with our results, both the left lateral orbitofrontal cortex and right insula have been implicated in norm-abiding social behaviour (Spitzer *et al.*, 2007).

The expression of normative social behaviours relevant to explore in bvFTD, as the human tendency to engage in fair, prosocial behaviour offers a window into one of the cardinal symptoms of the disease – reduced empathy. Our findings show that patients with lower levels of everyday empathic concern were more likely to reject unfair offers. Rather than being consistent with an elevated emotional response to unfairness or insensitivity to reward, we would suggest that this finding supports a diminished response to normative social expectations. This is consistent with a recent study illustrating that, in healthy individuals, trait levels of empathic concern predicts the tendency to engage in altruistic behaviour during a social interaction paradigm (FeldmanHall *et al.*, 2015). Objective assessment of empathy continues to pose a challenge in bvFTD, however our findings suggest that normative social behaviours on the Ultimatum Game may provide a useful surrogate for everyday empathy. As our current results are based on a single, clinical assessment of empathy, it will be important for future studies to undertake a more in-depth assessment of empathy. Given that empathy is a complex, multifaceted process that also draws upon other abilities that can be affected by

dementia including language, motivation and mentalisation (Decety *et al.*, 2012), future studies should explore the association between such abilities, different aspects of empathy, and how they relate to the expression of normative behaviour in neuropsychiatric conditions.

Considering our findings across the three scenarios of social norm compliance, expression of normative behaviour in the patients was not uniformly impaired. Engaging purely in fairness-based behaviour on the Ultimatum Game does not involve complex social computations. In contrast, engaging in prosocial or punishing behaviour relies on the effective integration of social contextual information to guide behaviour. Our finding that normative behaviour in the patients was disrupted when additional social processing was required is consistent with a recent hypothesis proposing that a range of symptoms in bvFTD may be underscored by a generalised deficit in the ability to effectively integrate social context and behaviour (Ibañez and Manes, 2012).

A potential limitation of our study design is that we did not include a control condition in the Ultimatum Game that incorporated additional information that was non-social, thereby being unable to directly distinguish whether the effects seen in the reappraisal conditions stemmed from social norm deficits, or simply difficulty in incorporating extra information. However, the inclusion of cognitive variables in our main analysis allowed us to control for the effects of cognitive dysfunction. Our results indicated that generalised cognitive dysfunction did not mediate patients' divergent performance in the social framing conditions – emphasising that our results are consistent with a specific deficit in integrating social context into decision-making. Nevertheless, future studies in bvFTD patients, and indeed in other neurodegenerative groups, which are matched for gender to control for potential

heterogeneity within the patient sample, are necessary to replicate and extend the results we describe here.

In conclusion, we have developed a novel neuroeconomic task to provide insights into complex social dysfunction in a neurodegenerative lesion model (bvFTD). In doing so, we have identified discrete deficits in patients' ability to integrate social contextual information to guide normative decision-making behaviour, associated with abnormalities in key fronto-striatal regions. This "social norm compliance" network represents an important target for future research into disordered norm compliance in bvFTD. From a wider theoretical standpoint, these findings speak to on going appeals that norm-based decision-making research be extended to clinical populations (Ruff *et al.*, 2013, Sanfey *et al.*, 2014), in an effort to determine causal mechanisms of social norm compliance, and its relevance to neuropsychiatric symptomatology across conditions.

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Figure legends

Figure 1 – Example of trials in the Ultimatum Game

Panel a) illustrates a trial in the baseline condition, where the participant has accepted the offer. Panels b) and c) illustrate trials from the prosocial and punishing social framing conditions where the offers were accepted and rejected, respectively.

Figure 2 – Baseline acceptance rates in the Ultimatum Game

Percentage of offers accepted in the baseline condition for fair versus unfair offer amounts. Error bars represent 95% confidence intervals.

Figure 3 – Social framing acceptance rates in the Ultimatum Game

Percentage of fair versus unfair offers accepted in the prosocial and punishing social framing conditions. Error bars represent 95% confidence intervals.

Figure 4 – Change from baseline acceptance rates in the social framing conditions

Panels show the change in acceptance rates from baseline in the social framing conditions, represented separately as fair (panel a) versus unfair (panel b) offer amounts. Error bars represent 95% confidence intervals.

Figure 5 – Voxel-based morphometry (VBM) correlates for change from baseline scores in the social framing conditions

Region of interest Voxel-based morphometry (VBM) results showing areas of significant grey matter intensity decrease correlating with a) Punishing – higher acceptance rates for unfair offers in the punishing condition (red-yellow), showing significant clusters in i) and ii) orbitofrontal/Subcallosal cortices; iii) anterior cingulate/paracingulate cortices; iv) right

inferior frontal gyrus; and b) Prosocial – lower acceptance rates for unfair offers in the prosocial condition (blue-light blue), showing significant clusters in i) left dorsal putamen; ii) right dorsal posterior putamen; iii) left anterior insula; iv) left lateral orbitofrontal cortex. Results uncorrected at $p < .001$ and at a cluster threshold of greater than 35 contiguous voxels.

Supplementary Figure 1 – Acceptance rates for each offer amount

Acceptance rates shown separately for offer amounts across the conditions. Error bars represent standard error of the mean. In the baseline condition, within both the patient and control groups, subjects demonstrated equivalent acceptance rates for 'fair' (\$5-\$5, \$6-\$4) offers (p values $> .3$). Both groups also showed equivalent acceptance rates across the 'unfair' (\$7-\$3, \$8-\$2, \$9-\$1) offers (p values $> .2$).

Supplementary Figure 2 – Voxel-based morphometry (VBM) showing regions of decreased grey matter in bvFTD patients

Region of interest VBM results showing areas of significant grey matter intensity decrease within the fronto-subcortical mask for bvFTD patients relative to controls. All results corrected for multiple comparisons (FWE) at $p < .05$ and at a cluster threshold of greater than 20 contiguous voxels. R = right hemisphere; L = left hemisphere.

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