

# BRAIN COMMUNICATIONS

## LETTER TO THE EDITOR

### The Interplay of Social Cognition Sub-domains in Frontotemporal Dementia

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Changes in moral processing occur frequently in frontotemporal dementia (FTD)<sup>1</sup> and represent one of several social cognitive domains that are affected in this population.<sup>2</sup> Recently, Strikwerda-Brown et al.<sup>3</sup> investigated moral reasoning in FTD using hypothetical scenarios consisting of moral dilemmas. To act on these, participants were presented a utilitarian action which they could either endorse or decline. Although the patients displayed normal probabilities of endorsing utilitarian actions, they felt less negative about their response, compared to controls. Interestingly, this group difference was specific for scenarios with a direct active involvement of the agent ('personal' dilemmas) and for which the proposed action contained a highly aversive emotional act ('high-conflict' dilemmas). The post-decision effect was associated with grey matter volume of the anterior temporal lobe (ATL), medial prefrontal cortex (mPFC) and insula (Ins). The blunted emotional response was associated with social conceptual knowledge and with the structural integrity of the uncinate fasciculus. Furthermore, the association between the emotional response and the structural integrity of the uncinate fasciculus was partially explained by social conceptual knowledge. The authors proposed that 'knowledge of social norms, stored in the ATL, is conveyed to the mPFC where it is incorporated in the production of an emotional response to personal, highly conflictual moral dilemmas'.<sup>3</sup>

Two previous FTD studies used the same set of moral dilemmas. Chiong et al. reported an increased utilitarian response bias specifically towards personal dilemmas. They also used functional MRI and revealed that the causal

influence from the salience network to the default mode network that they observed in healthy controls during moral reasoning, is significantly reduced in FTD.<sup>4</sup> We also visually presented these dilemma's verbally (18 non-moral, e.g. driving once or twice to bring home a number of plants; 11 impersonal, e.g. recommending an effective vaccine with a low probability of side-effects, 8 low-conflict, e.g. leaving an injured man by the side of the road to preserve leather upholstery of a car, and 13 high-conflict, e.g. smothering one's child in order to save oneself and others) on a computer screen and asked participants to indicate by a button press whether they would endorse a proposed action or not. We observed that moral changes in FTD are associated with facial emotion recognition abilities and resting-state activity in the main afferent node of the salience network, i.e. the anterior insula.<sup>5</sup> These findings support an interactive account among social-cognition sub-domains at the neural and psychological level. Here, we follow-up on the suggestions for future research by Strikwerda-Brown et al.<sup>3</sup> and investigate the association of moral reasoning with other social cognition domains. Furthermore, we performed a functional validation test of their structural connectivity findings. We re-analysed our FTD dataset and focused on high-conflict dilemmas.

Considering the modest sample size (controls:  $N = 19$ , 11 male; FTD:  $N = 12$ , 9 male), non-parametric testing was performed on the behavioural data. Between-group differences, within-group differences and associations were investigated by means of Mann-Whitney U tests, Wilcoxon Signed Rank tests and Spearman correlation coefficients, respectively. Voxel-wise whole-brain neuroimaging analyses

were thresholded at  $P_{\text{height}} < 0.001$  and minimal cluster size of 40 voxels.

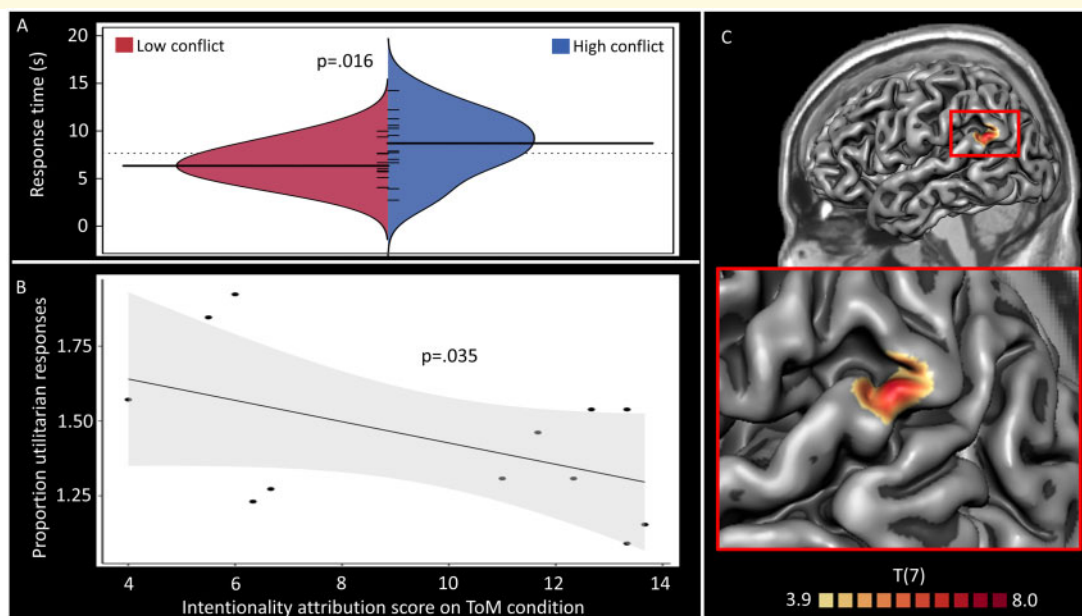
In addition to the probability of endorsing a utilitarian action, we used the mean reaction time as a proxy of Strikwerda-Brown's effect rating. We reasoned that longer reaction times reflect stronger emotional conflict and therefore labelled this measure as 'emotional conflict index'.

We first investigated the specificity of the emotional conflict index in the FTD sample and calculated the correlation with disease duration, executive processing speed as measured with the Trail Making Test part B and with the reaction time of the only other moral condition containing a direct active involvement of the agent (i.e. personal dilemmas), yet with only a slightly instead of a highly aversive emotional act, i.e. the low-conflict moral dilemmas. None of these analyses revealed a significant result (all  $\rho$ 's  $< 0.518$ ; all  $P$ 's  $> 0.102$ ), indicating it does not largely reflect overall disease progression, nor a domain-general executive or personal moral effect. Furthermore, while there was no significant difference between the control ( $N=19$ ) and FTD ( $N=12$ ) group on this measure ( $U=165$ ,  $P=0.117$ ), it was significantly increased compared to the low-conflict equivalent in the FTD sample ( $W=11$ ,  $P=0.016$ ; Fig. 1A), as expected.

To follow-up on the findings of Strikwerda-brown and explore the interplay between social cognition subdomains, we related utilitarian tendency as well as emotional conflict, with behavioural and neural characteristics.

First, we investigated the association between high-conflict moral reasoning and theory of mind (ToM). Twelve patients in our FTD sample completed the moral reasoning task and an implicit ToM task. The latter consisted of the Happé-Frith animation task designed to assess spontaneous mentalizing and has also been used by other groups in FTD.<sup>6</sup> The stimuli consist of videos showing moving geometric shapes (triangles). The task conditions consist of non-ToM (e.g. random movements) and ToM (dynamics display a ToM-like interaction between the triangle movements). The simple task instruction states to orally describe the stimuli and responses are scored according to the intentionality that is attributed to the kinematics of the triangles. The agreement among three independent raters who scored the answers was excellent (intraclass coefficients  $> 0.82$ ) (for details, see reference 7). We investigated the association between the high-conflict moral reasoning measures and intentionality attribution score of the ToM condition. This revealed a significant result with the utilitarian tendency measure ( $\rho(12) = -0.540$ ;  $P = 0.035$ , one-tailed), reflecting stronger utilitarian-based reasoning in FTD patients with lower mentalizing tendencies (Fig. 1B). The association between the intentionality attribution score of the ToM condition and the emotional conflict index was not significant ( $\rho(12) = 0.147$ ;  $P = 0.324$ , one-tailed).

Second, we investigated the association of the high-conflict moral reasoning measures with regional grey matter volume. All subjects were scanned on a 3 T MRI scanner,

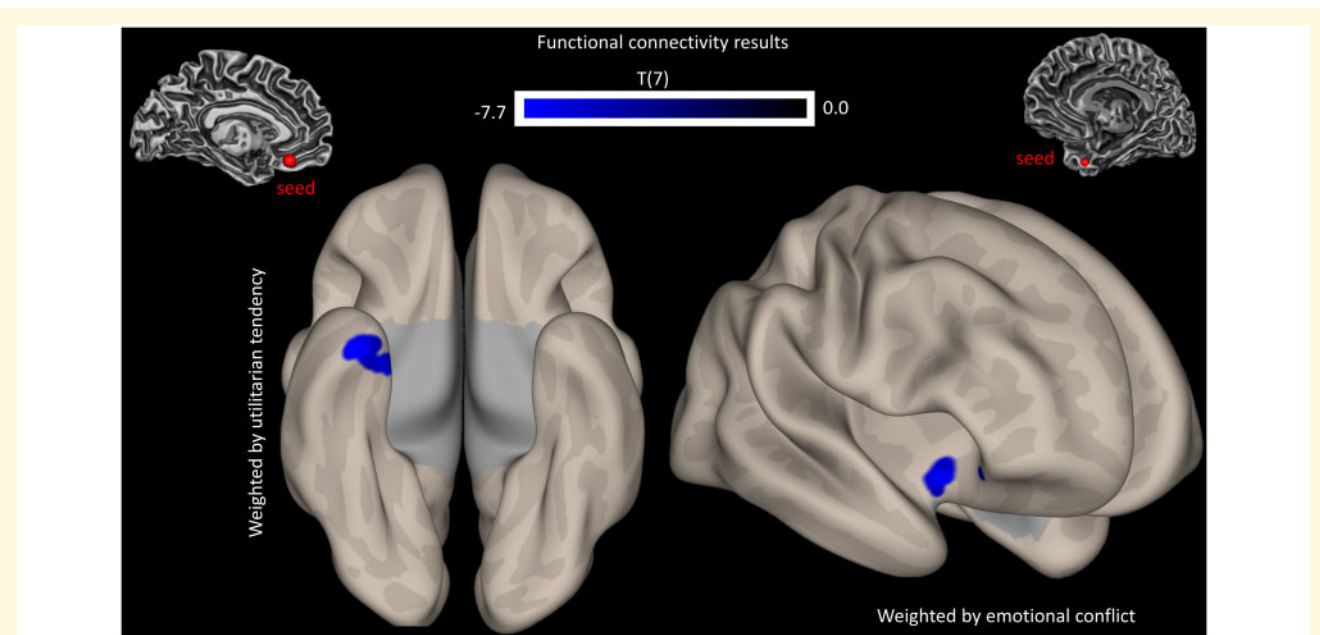


**Figure 1 Moral reasoning performance and associations.** (A) Split violin and rug plot displaying the response time as a function of emotional conflict. Thick lines indicate median, dashed line indicates the overall mean. Wilcoxon Signed Rank test:  $W = 11$ ,  $P = 0.016$ . (B) Scatterplot displaying the association between the proportion utilitarian responses and intentionality attribution score on the ToM condition of the Happé-Frith animation task. Spearman correlation ( $\rho(12) = -0.540$ ;  $P = 0.035$ , one-tailed). (C) Statistical map displaying regional grey matter volume associated with emotional conflict (response time during high-conflict moral dilemmas).

using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence [repetition time = 9.6 ms; echo time = 4.6 ms; matrix size =  $256 \times 256$ ; 182 slices; voxel size =  $0.98 \text{ mm}^3 \times 0.98 \text{ mm}^3 \times 1.22 \text{ mm}^3$ ]. These were analysed using SPM 12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK). The images were normalized to Montreal Neurological Institute (MNI) space and segmented into grey matter (GM), white matter and cerebrospinal fluid using default settings of the CAT 12 toolbox (<http://www.neuro.uni-jena.de/cat/>). Grey matter images were smoothed using a kernel with 8 mm full width at half maximum (FWHM). Associations between the moral high-conflict measures and grey matter volume in FTD were investigated by means of multiple regression analyses with age, sex and total intracranial volume as confound predictors. The emotional conflict measure was positively associated with a single significant cluster (peak:  $t(7) = 7.07$ , #voxels = 193; MNI:  $-60; -53; 23$ ) in the temporo-parietal junction, a region typically associated with mentalizing<sup>8</sup> (Fig. 1C). While these findings do not replicate the results of Strikwerda-Brown (possibly due to the within- versus across-group analysis discrepancy), they entail that patients with larger grey matter volume in a region of the mentalizing network, take more time to deliberate on high-conflict moral dilemmas. Utilitarian tendency was positively associated with a single cluster in the right inferior posterior temporal cortex (peak:  $t(7) = 7.48$ , #voxels = 57; MNI:  $53; -68; -15$ ).

Finally, we investigated whether we could validate Strikwerda-Brown's structural connectivity result at the functional level. We therefore re-analyzed the resting-state

functional MRI datasets (repetition time: 1700 ms; echo time: 33 ms; matrix size:  $64 \times 64$ ; field of view (FOV): 230 mm; flip angle:  $90^\circ$ ; slice thickness: 4 mm; no gap; axial slices: 32; 250 volumes; 7 min duration) from 11 FTD patients that took part in our moral reasoning study. Preprocessing consisted of realignment, unwarping, slice-time correction, outlier identification, direct segmentation, normalization and 4 mm functional smoothing according to the default settings of the CONN toolbox pipeline ([www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn), RRID: SCR\_009550). We focused on the ATL and mPFC regions reported by Strikwerda-Brown and investigated seed-based functional connectivity weighted by the two behavioural moral indices. Specifically, we defined 6 mm spherical regions of interest (ROIs) around the peak results that showed a negative correlation between grey matter volume and post-endorsement effect in the ATL (X; Y; Z MNI coordinates =  $27; 10; -37$  &  $-37; 7; -38$ ) and mPFC clusters (X; Y; Z MNI coordinates =  $6; 30; -16$  &  $-6; 30; -16$ ).<sup>3</sup> ROI-to-voxel whole-brain functional connectivity was computed as Fisher-transformed bivariate correlation coefficients. This revealed a significant negative correlation between proportion utilitarian responses on high-conflict dilemmas and connectivity between mPFC (seed region) and a cluster in the superior temporal gyrus (peak: MNI:  $-48; -22; -4$ ; #voxels = 44) and one in the ATL (peak: MNI:  $34; 0; -46$ ; #voxels = 144; Fig. 2). The latter result represents that weaker mPFC-ATL connectivity is associated with a stronger tendency for utilitarian reasoning, consistent with the hypotheses of Strikwerda-Brown. Surprisingly,



**Figure 2 Functional connectivity results.** Statistical maps displaying weighted seed-based functional connectivity, with a negative association between utilitarian tendency and medial prefrontal cortex (seed)—anterior temporal lobe functional connectivity (left) on the one hand and a negative association between emotional conflict and anterior temporal lobe (seed)—anterior insula functional connectivity (right).

we also observed a negative association between the emotional conflict index and functional connectivity between the ATL (seed) and a region in the anterior insula (aIns) (peak: MNI: 40; 18; -12; #voxels = 40;  $P_{\text{height}} < 0.001$ ), indicating that stronger emotional conflict links with weaker ATL-aIns connectivity (Fig. 2). While we expected a positive correlation, this finding may be compatible with an inhibitory ATL-aIns influence. There were no other significant weighted functional connectivity results.

In summary, the re-analyses of our dataset inspired by the findings of Strikwerda-Brown reveal that high-conflict moral processing is associated with mentalizing tendency, grey matter volume of the temporo-parietal junction, and with ATL-mPFC as well as ATL-aIns functional connectivity. These and previous findings reveal associations between deficits across social cognitive sub-domains like moral reasoning, social conceptual knowledge, mentalizing and visuo-social processing in FTD<sup>3,5</sup> and bear the question whether a single common factor may underly social cognitive sub-components, analogous to the so-called G factor underlying 'general' intelligence. Although not all social cognitive measures were significantly linked, which may relate to Type 2 errors in our modestly sized sample, the present findings may provide an incentive for setting up higher-powered confirmation attempts to address this hypothesis. While social cognition may not figure at the forefront of large-scale FTD initiatives like the FTD Prevention Initiative (FPI), Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat), Advancing Research and Treatment for Frontotemporal Lobar Degeneration-Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (ALLFTD) and the Genetic Frontotemporal Initiative (GENFI), they may be very helpful in addressing this hypothesis.

The combined neuroimaging findings further suggest key roles for the aIns, ATL, mPFC and temporo-parietal junction.<sup>3-5</sup> As these are associated with the salience (aIns), semantic appraisal (ATL) and default mode (mPFC and temporo-parietal junction) network, it seems unlikely that a single intrinsically connected functional network may constitute the neural substrate of a hypothetical general social cognition factor.<sup>9</sup> The findings of Chiong et al.<sup>4</sup> hint at the hypothesis that between-network influences could constitute a plausible underlying neural mechanism.

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## Data availability

Patient privacy issues preclude data sharing.

## Competing interests

The authors report no competing interests.

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