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# LETTER TO THE EDITOR

## Reply: Towards a neurocomputational account of social dysfunction in neurodegenerative disease

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Sir,

We have read the insightful letter by O'Callaghan and Hornberger (2016), wherein they propose a neurocomputational model for recent reports (Melloni *et al.*, 2016; O'Callaghan *et al.*, 2016) of social decision-making impairments in behavioural variant frontotemporal dementia (bvFTD). To follow up, here we outline a predictive, context-sensitive account of relevant mechanisms in bvFTD and other frontal disorders. First, we reanalyse our data (Melloni *et al.*, 2016) to characterize the neuroanatomical foundation of short-term strategies during social bargaining. Second, we propose a neurocognitive model addressing extant results and motivating predictions for further research on social negotiation.

In our study (Melloni *et al.*, 2016), participants played as proposers in a validated repeated version of the ultimatum game, making offers on how to split a sum of money with another player. Such a role brings together self-centred and other-centred processes, as one's own actions must be risk-assessed while predictions are made about the opponent's upcoming decisions. Capturing these complexities, our model characterizes successful social negotiation in terms of three dynamic strategies. First, self-benefits must be maximized through an adaptation to self-perspective (ASP). Second, the opponent's preferences and benefits must be acknowledged at each decisional step, via an adaptation to the other's perspective (AOP). Third, and more crucially, proposers must integrate their own perspectives with those of others to successfully deploy a self-other integration strategy (SOIS). While ASP and AOP constitute short-term strategies (as they are driven by the immediately previous offer), SOIS is a long-term strategy that unfolds throughout successive instances of negotiation. As shown in Melloni *et al.*, (2016), patients with bvFTD evinced normal short-term bargaining behaviour but they were impaired in long-term negotiation—which was also the case in patients with focal frontal damage.

Upon reanalysing the data, we found that preserved ASP performance in bvFTD correlated with the patients' grey matter volume in the right parahippocampal region and anterior temporal pole (Fig. 1A). Compatibly, these regions have been implicated in self-related episodic future thinking (Irish *et al.*, 2012), self-related information (van Veluw and Chance, 2014), and reinforcement learning of one's own positive

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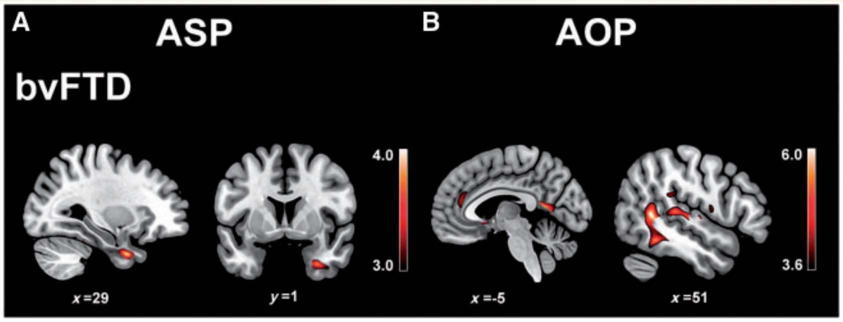


**Figure 1 Brain structural correlates of AOP and ASP in bvFTD.** (**A**) Correlation between ASP scores in bvFTD and the patients' grey matter volume in the right parahippocampal region and related anterior temporal lobe structures and ASP scores in bvFTD. (**B**) Correlation between AOP scores in bvFTD and the patients' grey matter volume in the left superior and middle temporal gyri, the bilateral precuneus, the left parahippocampus, the left insula, the left inferior frontal gyrus, and the left inferior orbitofrontal cortex. Data were reanalysed following the same procedure described in Melloni *et al.* (2016). For all regression analyses, we considered total intracranial volume and cognitive screening as covariates of no interest. The statistical threshold was defined as $P < 0.001$ (extent threshold = 50 voxels). For details about the task, related measures, and statistical procedures, see Melloni *et al.* (2016). ASP = adaptation to self-perspective; AOP = adaptation to the other's perspective.

outcomes (Katahira *et al.*, 2015). Both hubs have also been related with simulated outcomes in decision-making models (Hassabis and Maguire, 2007; Lee and Seo, 2016).

On the other hand, normal AOP scores in bvFTD patients was associated with grey matter density in key hubs of the social cognition network (Mar, 2011). These included the temporo-posterior structures (left superior and middle temporal gyri, bilateral precuneus, bilateral lingual gyrus, left parahippocampus) and insulo-frontal regions (left inferior frontal gyrus, left inferior orbitofrontal cortex, Fig. 1B).

Thus, the preservation of ASP and AOP strategies in bvFTD was associated with regions engaged in self-related anticipation of future outcomes and social cognition processes, respectively. Instead, frontal damage was associated with disrupted SOIS, indicating a specific impairment to integrate both short-term adaptive skills into a long-term negotiation strategy (Melloni *et al.*, 2016).

These results motivate the following neurocomputational model of social bargaining (Fig. 2). We propose that contextual adaptation for successful social negotiation requires intact deployment of both short-term and long-term strategies, as described below.

First, the proposer must develop an interactive tactic to maximize self-benefits, negotiating his/her potential earnings (Ruff and Fehr, 2014). We showed that this ability (ASP) depends on limbic regions (parahippocampal regions anterior temporal pole), which are involved simulated outcomes (Hassabis and Maguire, 2007; Lee and Seo, 2016). In bvFTD, these regions were critical for adequate performance, probably reflecting compensatory processes in relation to other more atrophied regions. Such areas thus seem critical for self-interests to flexibly adapt to changing bargaining scenarios. Indeed, parahippocampal activity directly supports retrieval of episodic memories required to simulate an action's consequences (Hassabis and Maguire, 2007).

Second, the proposer must also adapt to the other's preferences and benefits (AOP). This ability, preserved in bvFTD, partially relies on regions supporting the reduction of inequity to others (Tricomi *et al.*, 2010) and, more generally, on the social cognition network (Ruff and Fehr, 2014; Lee and Seo, 2016), indexed by posterior temporal, frontal, and insular regions (Mar, 2011). As AOP reflects the ability to mentalize and adapt our behaviour to others' perspectives, it is not unexpected for its main hubs to play critical roles in theory of mind, perspective taking (Saxe and Kanwisher, 2003; Buckner and Carroll, 2007; Kang *et al.*, 2013; Hutcherson *et al.*, 2015), and appraisal of others' behaviours (Billeke *et al.*, 2013; Suzuki *et al.*, 2015). Moreover, the medial prefrontal, orbitofrontal, anterior insular, and anterior cingulate cortices, together with the superior temporal sulcus, have all been related with the rejection of unfair offers (Sanfey *et al.*, 2003; Rilling *et al.*, 2004; O'Callaghan *et al.*, 2016), a canonical other-centred process.

Third, a successful long-term strategy (SOIS) seems to critically depend on the integrity of prefrontal regions (Nicolle *et al.*, 2012; Lee and Seo, 2016). Indeed, damage to such substrates correlated with selective SOIS impairments in bvFTD (Melloni *et al.*, 2016), a condition known to involve difficulties to integrate self-interest values with predicted preferences of second parties, thus undermining optimal social interaction (Seo and Lee, 2012; Lee and Seo, 2016; O'Callaghan *et al.*, 2016). We propose that this integration, and not necessarily the reliability of the information of others' preferences (O'Callaghan and Hornberger, 2016), is critical to explain the impaired bilateral interactions in frontal disorders. In fact, oscillatory activity during the anticipation of others' decisions seems to be a hallmark of long-term integration processes (Billeke *et al.*, 2015; Melloni *et al.*, 2016), reflecting the connectivity between temporo-parietal and prefrontal regions (Sadaghiani *et al.*, 2012; Billeke *et al.*, 2014*a*).

In brief, our model posits that predictive coding mechanisms subserving forward-looking inferences about incoming information at different neural levels. The value of the

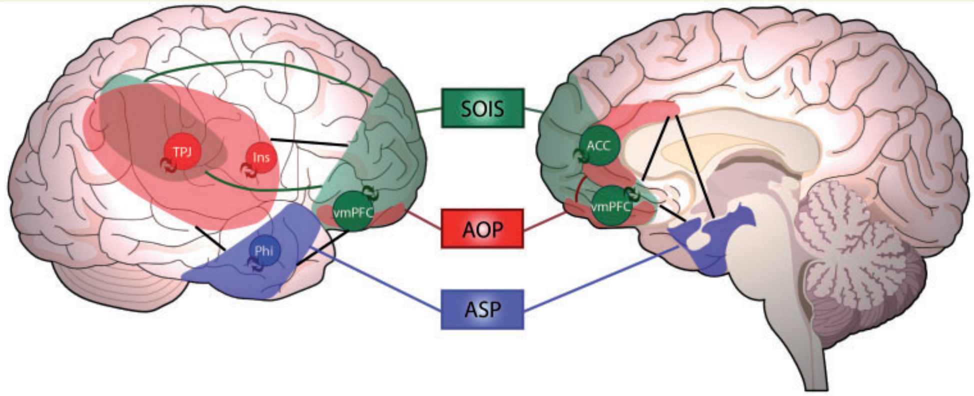


**Figure 2 A neuroanatomical model of social bargaining.** Social bargaining is proposed to involve an interplay among three mechanisms: ASP, AOP, and SOIS. (**A**) The system subserving ASP (the interactive tactic based on the maximization of self-benefits) relies on parahippocampal regions and the anterior temporal pole. These structures seem crucial to guide self-interests to immediately adapt to changing situations. (**B**) The system underlying AOP (the adaptation to the other's preferences and benefits) critically engages the social cognition network (posterior temporal, frontal, and insular regions). These hubs are related with mentalizing, adoption of other's perspectives, and appraisal of others' behaviours. (**C**) The system involved in SOIS (the context-sensitive and recursive integration of self-preferences with inferences about the other's choices in a long-term strategy) critically depends on prefrontal regions (ventromedial prefrontal and anterior cingulate cortices), with secondary involvement of temporo-parietal regions. The main hubs of the three systems are reciprocally influenced by feed-forward adjustments and active inferences along recursive interactions, mainly indexed by medial prefrontal regions in connection with temporo-parietal networks. These hubs also interact with other networks (not shown in the figure) related with reward and reinforcement learning. Strong colours indicate main hubs, whereas soft colours indicate fiduciary hubs. Same colour lines indicate within-system connections, and black lines indicate between-system connections. ASP = adaptation to self-perspective; AOP = adaptation to the other's perspective; SOIS = self-other integration strategy; TPJ = temporo-parietal junction; Ins = insular; vmPFC = ventromedial prefrontal cortex; Phi = parahippocampal; ACC = anterior cingulate cortex.

outcome of self-preferences is related with activation of anterior temporal regions supporting immediate adaptations to future behaviours favouring self-benefits. The value of the outcome of others' choices seems to depend on forward predictions based on both short-term inferences about the interactant (related to temporo-parietal networks) and one's own body signals indexing the salience of uncertainty regarding others' behaviours (related to insular networks). Finally, the long-term strategies indexing flexible adaptations during self-other integration depend on feed-forward adjustments along recursive interactions, mainly indexed by medial prefrontal regions in connection with temporo-parietal networks. The anterior cingulate cortex hub proposed by O'Callaghan and Hornberger (2016) probably participates in this process too. Anterior cingulate activity has been related to prediction errors regarding the others' outcome, but it is also involved in processes driven by self-benefits (Apps *et al.*, 2015). In fact, long-term adaptation during human interaction is marked by predicted error signals reflected in theta oscillation related to the anterior cingulate (Billeke *et al.*, 2014*b*). Note that some of these predictive coding principles have already been implicated in self-related processes (Seth, 2013), interoceptive and emotional signalling (Quattrocki and Friston, 2014; Barrett and Simmons, 2015), social cognition (Koster-Hale and Saxe, 2013; Van de Cruys *et al.*, 2014), and also long-term learning (Creutzig and Sprekeler, 2008). These active inference principles can be simulated to provide a fine-grained explanation of short- and long-term context-sensitive strategies during social negotiation. Impairments of contextual social cognition seem to be the hallmark of bvFTD and related frontal disorders. In fact, frontotemporal predictions updating contextual information, current states, and previous patterns of interaction lie at the core of the social context network model (Ibanez and Manes, 2012).

Our model accounts for current results and it motivates additional predictions. For instance, impairments of SOIS despite spared ASP and AOP skills should be mainly triggered by prefrontal damage, whereas the pattern should prove secondary and mitigated following insulo-temporo-parietal disturbances. The latter effect should be observed in patients with bvFTD or stroke with similar unilateral damage, as reported in Melloni *et al.* (2016). Note that, at the group level, these impairments seem to be explained by alterations in SOIS-related networks. However, at the individual level, they would be also partially related to disturbances of the social cognition network (Ibanez and Manes, 2012), the interceptive network (García-Cordero *et al.*, 2016), or the self-projection network (Irish *et al.*, 2011), each of which can impact different stages of social negotiation. The model also predicts that simple social norms (e.g. fairness) indexed by the social cognition network should be preserved in bvFTD, this population should evince deficits in more complex behaviours (e.g. prosociality, punishment) requiring integration of social contextual information via interactions among prefrontal structures and related circuitry. This, in fact, has already been demonstrated by O'Callaghan *et al.* (2016).

The model also implies novel predictions. If ASP is impaired in patients' featuring other conditions (e.g. anterior temporal stroke or disorders of the self), their negotiation patters should be biased towards the other's benefits, without developing a long-term increase of outcomes, and producing a flat long-term SOIS. Regions related to prospective memory or simulated personal outcomes, together with other reward and self-projection circuits, should yield reduced activation during self-perspective processes, thus enhancing inferences biased towards the interactant. On the another hand, if AOP is affected (as should be the case in autism spectrum disorder or schizophrenia), the social cognition network should provide incorrect or reduced inferences, which would induce unadjusted prediction errors and thus compromise long-term strategies. Indeed, the negotiation behaviour of schizophrenic patients with alterations in such circuitry diametrically opposes that of bvFTD patients (Billeke *et al.*, 2015). Finally, if hubs supporting both short-term and long-term strategies are affected, the model predicts not only an unsuccessful negotiation but also a random behaviour with high variability across offers. These effects can be modelled on current frameworks of associative networks spanning all three processes, together with (trial-by-trial and long-term) learning of Bayesian principles and statistical inferences. Also, the modelled effects can be contrasted with these outcomes in various neuropsychiatric conditions. If the model provides robust predictions confirmed by empirical results, specific recommendations could be advanced for intervention and training on specific short- and/or long-term strategies across a myriad of neuropsychiatric conditions. We are thus eager to further explore the possibilities of these extrapolations prompted by the valuable, synergistic proposal of O'Callaghan and Hornberger (2016).

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