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Neuropsychological and Neuroanatomical Correlates of the Social Norms Questionnaire in Frontotemporal Dementia Versus Alzheimer's Disease

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Abstract

Traditional neuropsychological batteries may not distinguish early behavioral variant frontotemporal dementia (bvFTD) from Alzheimer's disease (AD) without the inclusion of a social behavioral measure. We compared 33 participants, 15 bvFTD, and 18 matched patients with early-onset AD (eAD), on the Social Norms Questionnaire (SNQ), neuropsychological tests and 3-dimensional T1-weighted magnetic resonance imaging (MRI). The analyses included correlations of SNQ results (total score, overendorsement or "overadhere" errors, and violations or "break" errors) with neuropsychological results and tensor-based morphometry regions of interest. Patients with BvFTD had significantly lower SNQ total scores and higher overadhere errors than patients with eAD. On neuropsychological measures, the SNQ total scores correlated significantly with semantic knowledge and the overadhere subscores with executive dysfunction. On MRI analysis, the break subscores significantly correlated with lower volume of lateral anterior temporal lobes (aTL). The results also suggest that endorsement of social norm violations corresponds to the role of the right aTL in social semantic knowledge.

Keywords

social norms, behavioral variant frontotemporal dementia, anterior temporal lobe Alzheimer's disease, tensor-based morphometry

Introduction

Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease that originates in the frontal and temporal lobes with changes in personality, affect, and social behavior. Disinhibition with socially inappropriate behavior and a decline in social decorum is a major criterion for the diagnosis of bvFTD.[1] In contrast, patients with early Alzheimer's disease (eAD) may also have impaired social cognition but not to the extent seen in early bvFTD.[2] The greater deficits in social behavior in bvFTD compared to AD may be due to either structural or functional impairment of brain regions involved in social cognition. Traditional neuropsychological tests may be unable to detect these alterations in social behavior and may fail to distinguish bvFTD and eAD.[3] In addition, few studies have used measures dedicated for detecting changes in social behavior in order to distinguish these dementias, and the ones that have rely on informant-based measures,[4] which are fraught with observer interpretation and bias. Therefore, it is essential to include patient-based measures to evaluate social behavior in standard diagnostic procedures in order to differentiate these 2 dementias in early stages.

Although the Social Norms Questionnaire (SNQ) is part of the Frontotemporal Lobar Degeneration Module of the National Alzheimer's Coordinating Center database, one of the world's largest dementia databases,[5] there is sparse literature on the SNQ's psychometric properties and neural correlates. Two recent investigations found that patients with bvFTD

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scored worse on the SNQ while patients with AD performed similarly to controls.[6,7] A recent study, using the SNQ to assess deficits in social cognition in patients with schizophrenia and bipolar disorder, found that the SNQ relies on explicit knowledge about the world more than the social context in those psychiatric populations.[8] Further research is necessary for fully characterizing the properties of the SNQ.

The social norm adherence and violation aspects of the SNQ may involve different but overlapping regions of both the frontal and anterior temporal lobes (aTLs). The right lateral prefrontal cortex (lPFC) is involved in compliance to social norms,[9] and a decrease in medial prefrontal cortex (mPFC) volume is a strong predictor of rule violations, as reflected by performance on the Delis-Kaplan Executive Function System (D-KEFS) Tower Test.[10] The right dorsal (lPFC) and the lateral orbitofrontal cortex (OFC) may be activated in healthy individuals upon adherence to social norms on pain of punishment, suggesting that these regions show stronger activation in the presence of a social context.[11] The OFC is involved in the generation of expected socially appropriate behavior as well as the suppression of inappropriate behavior.[12] In addition, the right aTL may be responsible for maintaining knowledge of appropriate social behavior,[13] and the right temporal pole may have a role in the processing of empathy.[14] Taken together, these findings indicate that the neural substrates for the adherence to social norms may lie in the prefrontal, including OFC, cortex, and aTLs, with a possibility of right hemisphere dominance.

The purpose of the current study is 2-fold: to evaluate the SNQ as a measure to aid in the diagnosis of bvFTD and to characterize its neuropsychological and neuroanatomical correlates. Based on the literature, we focused our investigation on the frontal and aTL neuropsychological and neuroanatomical correlates of the SNQ. We were particularly interested in whether there are differences in the correlates of the 2 types of errors on the SNQ, overadherence, and break. We hypothesize that right frontal functions and localization correspond to inappropriate overadherence to social norms and that right anterior temporal functions and localization correspond to social norm violations or break errors.

Materials and Methods

Participants

A total of 33 participants, 15 with bvFTD and 18 with eAD, were recruited from an outpatient behavioral neurology clinic in an academic university medical center. Participants with BvFTD met criteria for "probable" bvFTD based on revised International Consensus Criteria[1] by history reported by caregivers and findings on neuroimaging. Participants with AD were diagnosed according to the National Institute of Aging-Alzheimer's Association criteria for clinically probable AD.[15] In order to provide a matched cohort with the bvFTD group, patients with AD were comparable in age, age of onset, duration after the onset, years of education, ethnicity, gender, and global cognitive functioning on the Mini-Mental State Examination (MMSE; see Table 1).[16] Although the Clinical Dementia Rating (CDR) scale-Sum of Boxes is a functional measure that is not as memory dependent as the standard CDR score, it was not used to match the dementia groups because it does not take into account the differences in language and behavioral disturbances between the populations with bvFTD and AD. None of the patients with AD had previous histories of psychiatric disorders or neurological diseases. Across both groups, individuals with major medical illnesses (except hypertension or diabetes) were excluded. The study was reviewed and approved by the local institutional review board (IRB), and study participants were enrolled according to IRB guidelines.

Table 1. Demographic Information.

N = 33	bvFTD N = 15	AD N = 18	*P*
Age, y	60.1 (11.2)	59.9 (5.5)	ns
Age of onset, y	55.7 (9.9)	56.1 (6.6)	ns
Years of onset, y	4.4 (4.1)	3.7 (2.3)	ns
Edu, y	15.3 (2.1)	16.4 (1.8)	ns
MMSE	23.4 (6.8)	24.6 (4.2)[a]	ns
Gender	7 F (46.7%)	12 F (66.7%)	ns[b]
CDR Sum of Boxes, $p<.001$[c]	7.4 (2.4)	3.9 (1.9)	

Abbreviations: AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; ; Edu, education; MMSE, Mini-Mental State Examination; ns, not significant.
[a]One participant unable to complete MMSE.
[b]Chi-square.
[c]95% CI: 1.83-5.015.

We used the 22-item version of the SNQ and its subscales as a measurement of social behavior and correlated them with neuropsychological tests conducted by a neuropsychologist that were selected based on established neuroanatomical correlations with prefrontal and aTL regions. We originally analyzed data from 29 participants who had both SNQ scores and neuroimaging data (bvFTD = 13 and eAD = 16). Missing data were excluded (bvFTD = 2 and eAD = 2) from the analyses. We further excluded one additional participant with bvFTD because this participant's tensor-based morphometry (TBM) data had unexpectedly high gray matter volume in both the temporal and frontal regions and thus was an outlier in our sample. The remaining data from 28 participants (bvFTD = 12 and eAD = 16) were included in the final analyses.

Measurement of Social Behavior, Functional Impairment, and Neuropsychological Testing

Social norms questionnaire. The measure is a 22-item "yes" or "no" questionnaire given to the patient to detect inappropriate social behavior in hypothetical scenarios. Written directions are "The following is a list of behaviors that a person might engage in. Please decide whether or not it would be socially acceptable and appropriate to do these things in the mainstream culture of the United States and answer yes or no to each. Think about these questions as if they were occurring in front of or

with a stranger or acquaintance, NOT a close friend or family member." For example, "would it be socially acceptable to wear the same shirt twice in two weeks?" A total score is obtained by summing correct items (22 possible). A higher total score indicates greater knowledge of social norms. Two subscales are calculated: "Overadhere" errors and "Break" errors. Overadhere errors refer to endorsement of a socially appropriate behavior (ie, wearing the same shirt twice in 2 weeks) as inappropriate. Break errors refer to endorsement of a socially inappropriate behavior (ie, eating pasta with your fingers) as appropriate. Reliability and validity of the SNQ are not yet established. (The SNQ was used with permission from Katherine Rankin, PhD, the developer of this instrument).

Pyramids and Palm Trees test. The Pyramids and Palm Trees test (PPT)[17] is a 52-item measure of nonverbal semantic memory. For our study, the picture version of the PPT was used: 2 pictures were presented below a target picture, and participants were asked to identify the picture that best matches the target item conceptually. Preliminary TBM studies indicate that while verbal decline in semantic knowledge is characterized by a left hemispheric dominance, nonverbal semantic memory decline appears to be correlated with right frontotemporal atrophy.[18]

Wisconsin Card Sorting Test. The Wisconsin Card Sorting Test (WCST)[19] consists of 4 key cards with a total of 128 response cards with differing geometric patterns. The participant's task is to sort the cards according to different principles, but they are not instructed to sort the cards in a particular manner. Thus, the WCST is a measure of set-shifting abilities—that is, the ability to change responses based on changes in the environment—as well as a measure of perseveration, defined as repeatedly making errors previously labeled as incorrect. Based on lesion studies,[20,21] the WCST has been regarded as a measure of frontal lobe dysfunction, as patients with prefrontal and dorsolateral prefrontal lesions perform worse on this measure. In our study, we utilized numerical categories (rule recognition and abstraction abilities), trials (how fast participants can evaluate the context), perseverative errors, and preservative responses (ability to set shift).

Delis-Kaplan Executive Function Scale. The Delis-Kaplan Executive Function Scale (D-KEFS)[22] consists of 9 subtests, designed to test many verbal and nonverbal executive functions. It is thus widely used as a measure of frontal lobe dysfunction.[23] In our study, we are using the DKEFS design fluency test, in which participants are asked to draw designs connecting filled dots only, followed by doing the same task except with empty dots, and then finally switching between empty dots and filled dots. This specific subtest of the DKEFS is designed to test mental flexibility and the ability to generate a rule and adhere to it when appropriate.

The FAS test,[24] included in the DKEFS set of subtests, asks participants to verbalize all of the words that come to mind that begin with the letter "F" in 60 seconds, followed by the letter "A" and letter "S." This test measures phonemic word fluency, a subtype of verbal fluency. Retrieval of these words starting with the given letter requires mental flexibility and mental set shifting abilities.

Neuroimaging Data Acquisition, TBM, and Diffusion Tensor Imaging Analysis

The participants underwent magnetic resonance imaging (MRI) using a standardized protocol on the same 1.5 Tesla Siemens Avanto MRI scanner. High-resolution T1-weighted 3-dimensional (3D) MRI scans were acquired in the coronal plane using a Magnetization Prepared Rapid Gradient Echo sequence with the following acquisition parameters: repetition time = 2000 ms, echo time = 2.49 ms, inversion time = 900 ms, flip angle = 8°, slice thickness = 1 mm, 25.6 cm field of view, voxel size = $1.0 \times 1.0 \times 1.0$ mm^3. An automated brain surface algorithm (BSE) was applied, along with manual editing to generate a deskulled brain volume with the scalp, dura, and meninges removed. To adjust for global differences in brain positioning and scale across individuals, all scans were linearly registered to the stereotaxic space defined by the International Consortium for Brain Mapping[25] with a 9-parameter transformation. Globally aligned images were resampled in an isotropic space of 230 voxels for each axis (x, y, and z) with a final voxel size of 1 mm^3.

To quantify 3D patterns of volumetric brain differences for each participant, an individual change map, or Jacobian map, was computed by nonlinearly registering each individual scan to a template using a nonlinear inverse consistent elastic intensity-based registration algorithm, with a built-in smoothing kernel, driven by a mutual information-based cost function (3D MRI), which has been previously described.[26] For each participant, a map of the Jacobian determinants was computed from the gradient of the deformation field to illustrate the voxel-wise expansion or contraction factors of relative volume differences between each individual's regions of interest (ROIs) and the templates.

Removal of the skull and other nonbrain tissue (ie, scalp, dura, and meninges) was achieved with an automated BSE and manual editing using BrainSuite software (version 11).[27,28] All algorithms used in creating TBM Jacobian maps, including linear registration, nonlinear registration, and linear regression algorithms, were developed at the Laboratory of NeuroImaging (LONI) and have been successfully used in previous studies measuring brain volumetric changes in neurodegenerative disorders[29,30] and were implemented using the LONI pipeline.[31]

Statistical Analysis

All TBM data, including ROIs, were analyzed with SPSS version 20. Testing for distribution of data used the Shapiro-Wilk test. Student t test and Mann Whitney U test were used for comparison of means between 2 groups. Partial Pearson correlations were conducted between the SNQ total scores, break errors, and overadhere errors with 6 frontal and temporal brain ROIs in each hemisphere, including dorsolateral prefrontal

cortex (DLPFC), OFC, lateral aTL, medial aTL, medial temporal lobe, and ventricle, from each hemisphere, to explore neural correlations of grey matter. We did not correct statistical power for multiple comparisons because we performed partial correlation analyses with ROIs selected a priori.

Results

Demographic Data

There were no significant differences between bvFTD and AD groups in terms of gender, estimated age of onset, duration of illness, years of education, or MMSE score (Table 1). Caregivers of the bvFTD group reported significantly higher sum-of-boxes scores on the CDR Scale ($P = .001$),[32] indicating greater functional impairment.

SNQ score

The eAD group had a higher mean total SNQ score compared to the bvFTD group ($P < .001$; Table 2). This is largely attributed to significantly higher overadhere errors in the bvFTD group ($P = .002$), whereas there were no significant differences between groups in break errors.

After controlling for age and diagnosis, there were significant correlations between the SNQ and 4 widely used neuropsychological tests (PPT, WCST, DKEFS, and FAS test; Table 3). The SNQ total score was positively correlated with the numerical categories score on the WCST ($r = .491$, $P = .033$), the PPT total score ($r = .481$, $P = .010$), and the FAS score ($r = .483$, $P = .042$) and was negatively correlated with WCST trials score ($r = -.479$, $P = .033$). The number of overadhere errors was negatively correlated with the numerical categories score of WCST ($r = -.549$, $P = .015$), positively correlated with the WCST trials score ($r = .571$, $P = .009$), and negatively correlated with DKEFS design fluency switching score ($r = -.536$, $P = .007$). There were no significant correlations between the SNQ break errors and performances on any of the neuropsychological tests.

After controlling for age and diagnosis, higher break errors were correlated with lower combined volume of both lateral aTL ($r = -.435$, $P = .026$). When analyzing each hemisphere separately, the correlation demonstrated a strong trend in the right aTL ($r = -.382$, $P = .054$), but not in the left aTL ($r = -.296$, $P = .234$). The higher break errors were also correlated with enlargement of ventricles on both sides ($r = .401$, $P = .042$), but again predominantly on the right ($r = .443$, $P = .024$) and not on the left ($r = .311$, $P = .122$; see Figure 1). There were no significant correlations between either SNQ total score or overadhere errors with brain volume in any of the ROIs.

Table 2. Means and Standard Deviations of SNQ Scores Categorized by Group of Diagnosis.

N = 33	bvFTD N = 15	AD N = 18	*P*
Total score	15.9 ± 2.9	19.4 ± 1.5	<.05[a]
Overadhere errors	4.6 ± 2.9	1.6 ± 1.5	<.05[a]
Break errors	1.5 ± 1.4	1.1 ± 1.3	ns

Abbreviations: eAD, early Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia.
[a]Using Mann-Whitney *U* tests, bvFTD, and eAD.

Table 3. Correlation Coefficients (*r*) Between SNQ Scores and Neuropsychological Tests.

Neuropsychological Tests (N = 28)	SNQ Total Score	SNQ Break Score	SNQ Overadhere Score
D-KEFS-design fluency scores			
Filled dots	0.354	−0.053	−0.329
Empty dots	0.322	−0.04	−0.301
Switching	0.57[a]	−0.091	−0.536[a]
WCST scores			
Total score	0.279	0.113	−0.332
Perseverative response	−0.296	−0.329	0.429
Perseverative errors	−0.278	−0.325	0.409
Numerical categories	0.491[a]	0.116	−0.549[a]
Trial	−0.479[a]	−0.209	0.571[a]
PPT total score	0.481[a]	−0.188	−0.384[a]
FAS	0.483[a]	−0.193	−0.35
F words	0.359	−0.045	−0.321
A words	0.536[a]	−0.209	−0.394
S words	0.496[a]	−0.285	−0.302

Abbreviations: SNQ, Social Norms Questionnaire; D-KEF, Delis-Kaplan Executive Function System; WCST, Wisconsin Card Sorting Test; PPT, Pyramids and Palm Trees test.
[a]$P < .05$ of Pearson's correlation coefficient when controlling for age and diagnosis group.

Discussion

This study has 3 main findings: First, the bvFTD group has lower SNQ total scores and committed more overadhere errors compared to the AD group. This finding suggests that the SNQ is helpful in distinguishing these 2 dementias. Second, the overadhere errors correlate with neuropsychological testing associated with frontal executive deficits. Third, the break errors, which represent endorsing inappropriate behaviors, correlate with lower volume in the lateral aTL, particularly on the right. Together, these findings suggest different neuropsychological and neuroanatomical aspects of these 2 types of social norm violations among patients with dementia and bvFTD.

Behavioral variant frontotemporal dementia is characterized by impairments in social cognition. Memory and other cognitive functions remain relatively intact early in the course of the disease.[1] These patients frequently have dramatic changes in personality with prominently impaired social interactions, which cause discomfort in others.[33] Behavioral disinhibition with socially inappropriate behavior, loss of manner and graces, decreased decorum, and decreased emotional expression are examples of typical behavioral symptoms in bvFTD.[1] Given their social behavioral changes and the relative insensitivity of traditional neuropsychological measures

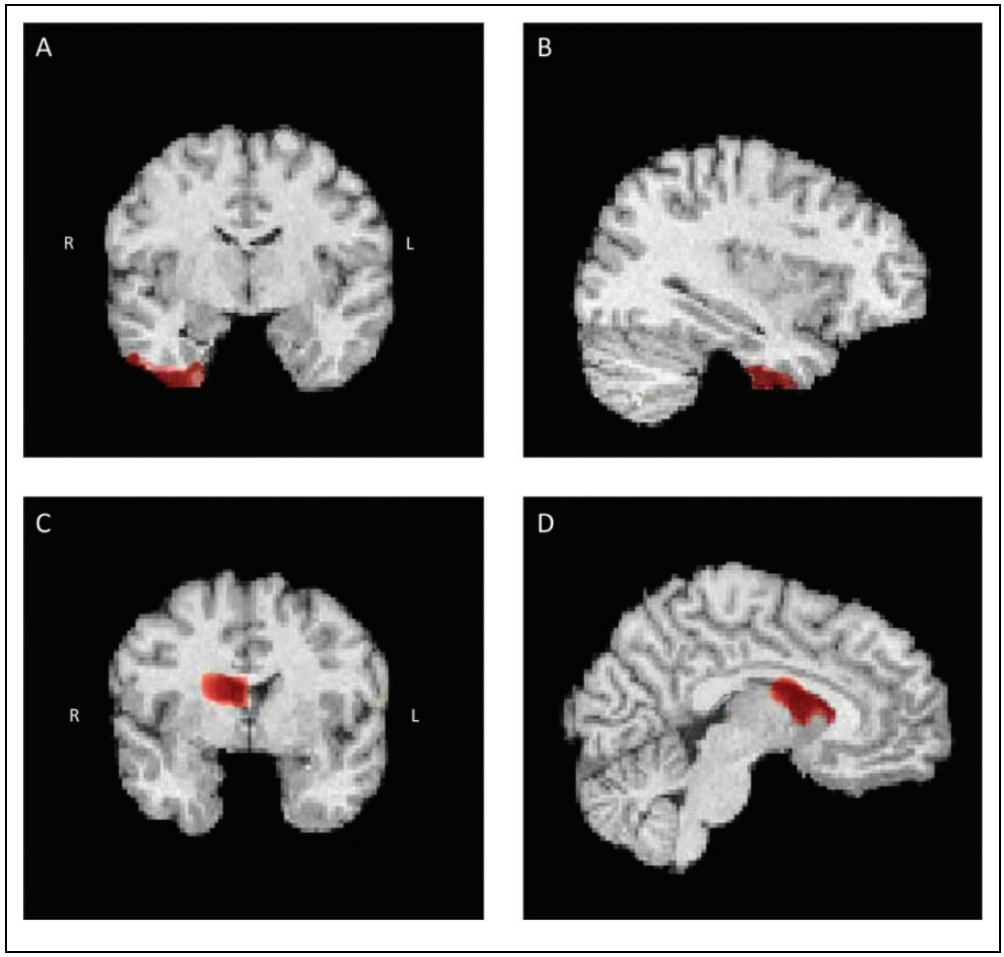

Figure 1. Neural correlates of break score.

for early bvFTD, a rating scale for measurement of social behavior tendencies can be very helpful in the initial diagnosis of this disease.

This study indicates that both total score and overadhere errors of the SNQ can differentiate bvFTD from AD, and that the total SNQ score may reflect aspects of both frontal and aTL dysfunction, as reflected in disturbances on verbal fluency and semantic knowledge, reflected by performance on the PPT. Higher overadhere errors are particularly associated with frontal dysexecutive deficits including decreased rule recognition (numerical categories score of WCST), decreased ability to perform set/rule shifting (DKEFS design fluency switching score), and increased number of trials to finish a task (WCST trials score). These results correspond with findings from previous literature, in which patients with bvFTD demonstrate impairments in abstract thinking, mental flexibility, and the evaluation of context.[1,34] For example, common overadhere errors in the bvFTD group were answering "no" to the following scenarios concerning whether or not they were socially appropriate gestures: "tell a coworker your age," "eat ribs with your fingers," and "tell a coworker you think they've lost weight. These findings suggest that overadherence to social norms results from frontal lobe deficits with difficulty recognizing the changing context of a rule and changing responses appropriately. Given that the TBM analyses did not show significant DLPFC and OFC differences on overadherence errors, these errors may reflect greater executive functional deficits rather than detectable structural changes on neuroimaging.

Social norm violations, as reflected in the break errors, may have a different mechanism and source than the overadhere errors. Although patients with bvFTD usually have greater behavioral disinhibition than patients with eAD, we did not find more break errors in the bvFTD group, possibly because the tendency to overadhere suppressed the tendency for social norms violations. The absence of significant correlations between the break errors and performance on the neuropsychological tests may be due to a lack of sensitivity in the detection of impaired social behaviors and deficits in social cognition by traditional neuropsychological measures. However, the correlations of break errors with an enlargement of the right ventricle and a smaller right aTL volume support the hypothesis that the aTL is not only a "semantic hub" for conceptual processing[35] but may also be involved in social semantics and higher social function through connections with the medial frontal cortex, OFC, and amygdala.[36] Recent functional studies in

humans have consistently shown that the aTL plays a chief role in social reward dependence,[37] perception of feelings of others,[38] and interpersonal warmth.[39] Both aTLs are activated during retrieving and registering a new social association word,[40] and social semantics, an understanding of social concept words such as "honor-brave," are associated with activation of bilateral aTLs.[41,42] In patients with bvFTD, hypometabolism in the aTL, especially on the right, may result in disproportionate impairments in understanding social concepts compared to nonsocial concepts.[13] Overall, these studies support the hypothesis of social semantics localized in the aTL, particularly on the right, with loss of volume or overall dysfunction in that region facilitating violations of social semantics or elevated break errors on the SNQ.

This study has strengths and limitations. First, the SNQ is geared specifically toward US culture. At this point in time, the SNQ cannot be generalized to other societies where the range of accepted social behavior differs from the United States. Second, the neuropsychological battery and neuroanatomical ROIs used in this study were limited to the frontal and temporal regions. Lastly, our study involved a relatively small sample size. Nevertheless, we had significant findings with this number of participants. Further studies are needed to establish the correlations between the SNQ and the neuropsychological and neuroimaging measures.

In conclusion, this study showed that patients with bvFTD had higher SNQ scores and committed more overadhere errors compared to the eAD group. Their overadhere errors correlated with deficits of frontal executive processes, particularly in changes of rule-based behavior consequent to changes in context. A greater endorsement of social norms violations or break errors in the total sample was associated with reduced volume in the aTL, particularly in the right hemisphere, and may correspond to disturbance in social semantic knowledge. The findings of this study are preliminary but can lead to further research exploring the different mechanisms involved in social norm interpretation and adherence and the different parts of the frontal and aTLs involved in these mechanisms.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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