Title: Disorders of emotional processing in amyotrophic lateral sclerosis

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Abstract

Purpose of review. Amyotrophic Lateral Sclerosis (ALS) is a degenerative brain disease characterized by motor, behavioural and cognitive deficits. Only recently, emotional processing disorders have been shown in this disease. The interest in affective processing in ALS is growing given that basic emotion impairments could impact copying strategies and mood.
Recent findings. Studies explore both basic emotion recognition and social cognition. Results are congruent on arousal and valence detection impairments, independently from the stimulus modality (verbal or visual). Further, recognition of facial expressions of anger, sadness and disgust is impaired in ALS, even when cognition is preserved. Clinical features such as type of onset and severity of the disease could be the cause of the heterogeneity in emotional deficits profiles between patients. Finally, a study employing diffusion tensor imaging showed that emotional dysfunctions in ALS are related to right hemispheric connective bundles impairments, involving the inferior longitudinal fasciculus and the inferior frontal occipital fasciculus.

Summary. Research on emotional processing in ALS is still in its infancy and results are mixed. Future research including more detailed clinical profiles of patients and measures of brain connectivity will provide useful information to understand heterogeneity of results in ALS.

Keywords: emotion recognition, facial emotion expressions, social cognition, amyotrophic lateral sclerosis, bulbar onset.
**Introduction**

Along with cognitive deficits, emotional impairments undermine personal identity and hamper the ability to cope with everyday life social tasks [1, 2]. Emotional processing requires the integrity of sensory systems and higher cortical areas that link online information to the knowledge we already
possess and that modulate emotions [3, 4]. Studies on healthy subjects and patient works show that the emotional network comprises both cortical, such as insular, temporal and orbitofrontal cortices, and subcortical structures, including the amygdala [3, 4]. Consequently, a number of necessary "stations" to process emotions exists within the brain that are susceptible to damage. Not surprisingly, research in the past years provided convincing evidence that degenerative diseases such as Alzheimer Disease and Fronto-temporal Dementia (FTD) are characterized not only by cognitive deficits but also by widespread impairments in basic emotion recognition and in higher emotional abilities [1, 5-7].

Less intuitively, very recent studies proven that even degenerative brain diseases primarily impacting motor abilities can be characterized by emotional impairments. A striking example is Amyotrophic Lateral Sclerosis (ALS) [8]. Initially depicted as a pure motor neuron disease, ALS is now known to cause also non-motor impairments such as cognitive deficits [9*]. In some cases symptoms include deregulated behavioral manifestations [10] that in around 15% of patients occur as a frank manifestation of dementia [11].

Anatomical and structural studies on ALS in the 1990s highlighted pathological findings (such as ubiquitin immunoreactive inclusions, neuronal loss and gliosis, hypometabolism) in the amygdala, the parahippocampal cortex and in the insula [12-14], suggesting that ALS might also feature emotional processing impairments. However, the first experimental investigations on basic emotion recognition and social cognition are dated back to 2005 [15, 16]. Thus, research on emotional processing in ALS is quite young, with only 13 papers published in 9 years (see Table 1 for a summary of the studies).
This review, provides a summary of the findings concerning emotional processing in ALS, concentrating on basic recognition and theory of mind related studies. It is of uttermost importance to understand whether emotional processing is intact in ALS, as this factor might affect directly disease copying strategies and quality of life [28].

**Visual emotional material processing: Facial Emotion Recognition (FER)**

Examination of primary facial expressions of emotions recognition usually employs the Ekman & Friesen dataset of facial expressions [29], requiring subjects to match a facial expression with a label that can be chose among a fixed number of alternatives [30*]. A closer inspection of the 4 studies using the classic full displays of the Ekman & Friesen dataset of facial expressions in ALS reveals a compromising in anger, sadness and disgust recognition (3 over 4 studies confirm this finding). Conversely, happiness and fear recognition is impaired only in 1 study [23]. Noticeably, studies suggesting impairments in FER are used to advocate for the parallel between behavioral FTD (bvFTD) and ALS [23, 17**]. However, fear recognition is compromised in 6 over 8 eight studies when considering the same task in bvFTD patients [1]. This result highlights that differences subsist between ALS and FTD concerning emotional processing. It has been proposed that cognitive impairments would explain the presence of emotional deficits and differences between patients [18*]. However, the only available study [18*] contrasting demented and not demented patients on FER used caricatures of emotional expressions, which are easier to be recognized and do not allow to exclude impairments in cognitively preserved individuals [17**]. Further, a very recent study show that FER impairments are present in cognitively unimpaired ALS patients [17**] suggesting that the explanation for the diversity of results might reside in a different factor, either methodological (task difficulty) or clinical. For instance, in the Crespi et al. [17**] study, 4 patients within the overall sample present with a bulbar onset, while in the Savage et al. [18*] study, 13
bulbar onset patients compose the vast majority of the group with a concomitant diagnosis of FTD and resulting impaired at the emotional task. The diverse onset might implicate a different involvement of frontal brain areas, leading to heterogeneous impairments. Such diversity in fact, has already been proven for cognitive deficits in ALS, supporting the idea that the presence of pseudobulbar palsy influences the type of dysfunctional patterns that might present [31]. Similarly, it is not known whether functional impairments indicative of disease severity are comparable between the two studies, as this data is not reported in the Savage et al. study [18*]. In summary, it is possible that diverse clinical features intrinsic to the pathology and related to the disease progression and onset might justify incongruent results.

The very recent findings from the Crespi et al. study [17**] suggest a structural explanation for the diversity of results. This study is the first analysis of white matter connectivity in ALS in relation to emotional processing. Findings indicate impairments in right hemispheric ventral associative bundles: in the inferior longitudinal fasciculus, which connects the occipital cortex with temporo-limbic regions and is implicated in face recognition [32], and in the inferior frontal occipital fasciculus, which subserves conscious vision [33] through top down mechanisms related to detection and retrieval of the emotional value of stimuli. These findings support the fascinating hypothesis that different degrees of disconnection between areas crucial for emotional processing would account not only for diversity across studies but would also justify the differences between bvFTD and ALS (especially concerning fear processing). In the first case, atrophy could directly damage emotional structures since the beginning, resulting in more diffuse and generalized impairments, while in the latter condition a weaker connection between structures in association with atrophy would give rise to a more heterogeneous pattern of impairments.

**Visual emotional material processing: scenes**
Lulè and co-workers employed standardized emotional images to assess arousal, emotional valence, and association of movement together with physiological parameters in ALS [15]. More recently, this same group explored functional changes in brain networks in ALS patients, performing the only available follow up study on emotional processing up to now [26]. The first study [15] showed inconsistent results from physiological parameters, too general to be interpreted. Behavioural findings on the other hand highlighted that ALS patients rate pictures as more positive in valence, regardless of the real valence, and calm and neutral scenes as more arousing than controls. No differences are highlighted in terms of association of movement. These findings are firstly interpreted as a positive and emotionally balanced disposition of patients regardless of their disease, as the Authors do not find correlations with frontal lobe dysfunctions as measured through neuropsychological testing [15]. The second study compares ALS patients, healthy controls and tetraplegic patients on a 6 months period, on the same measures of valence and arousal, monitoring also brain responses [26]. Results show that ALS patients present an increased response in the right supramarginal area and a reduced response in extrastriate visual areas compared to healthy controls but not to tetraplegic patients. Further, responses in the anterior insula are reduced at follow-up. These findings are interpreted as a reduced arousal at the neural and behavioural level, with the progression of the disease. Moreover, the Authors reason that the behavioural responses found in ALS patients in their previous study [15] could have also indicated that sensitivity to social-emotional cues is altered in these patients [26]. Taken together, the results from these two studies suggest a compromising in valence and arousal detection in emotional scenes grounded on dysfunctional brain activity in both hemispheres.

**Verbal emotional material processing: prosody and words**
Results on emotional processing from prosody in the few studies exploring this topic are mixed. One study highlights a general compromising for all emotional categories [25], while the other highlights that emotional processing is generally spared with the exception of surprise, but only in those patients that are also impaired in FER [27]. The task used by Meier et al. [25] is a validated battery. Importantly, in the comprehension part of this battery, individuals are asked to match a sentence to a label composed by an emotional face and a word that depicts an emotion, among six alternatives. On the other hand, the Zimmerman et al. study [27] employs ad hoc developed stimuli and requires participants to match a sentence to a semantic label only. From the description of the two tasks, it is evident that the one employed in [25] might be more difficult for ALS patients as the answer modality involves facial expressions. Secondly, the sample size is bigger in [25] than in [27]. Finally, the two studies enrolled clinically different populations: in one study the onset is not specified and disease duration is on average 34.56 months [25], while in the other only individuals with bulbar onset are included and disease duration is not specified [27]. As for FER impairments, clinical variables might be precious to understand differences between studies also for prosody.

Concerning semantic processing of emotions lateralized left-hemispheric activations in the inferior frontal gyrus for words with a negative valence have been found using a pleasant/unpleasant word task in combination with functional magnetic resonance imaging (fMRI) [24]. Secondly, a difference in ratings between positive and negative words in ALS patients is also suggested by a subsequent study that evaluates emotional memory [21].

Taken together, these findings support the idea of an altered processing of arousal in ALS [26], not restricted to visual but involving also verbal material [21, 24]. Results on prosody [24] on the other hand are much less clear and do not allow final conclusions.
Memory for emotional material

Since now, two studies explored memory for emotional material in ALS patients. Of note, one is the work of Papps and colleagues [16], which has pioneered emotional processing research in ALS. The other is the more recent study by Cuddy and co-workers [21]. It is of note that results are divergent between studies even though they adopted almost the same task. Papps et al. [16] found that ALS patients do not show enhancement of memory for negative words. However, the subsequent study [21] do not present such a group difference, rather is able to highlight differences between healthy controls and patients only when taking into account single individuals that score below the 5th percentile. Contrasts in findings are explained by the heterogeneity of profiles across ALS patients, by a difference in depression scores that characterized the group of patients in the first study, or by methodological differences in the version of the adopted task [21]. The Authors conclude that their findings might not indicate a specific alteration in memory for emotional material but rather a general impairment in memory. However, in addition to the differences noted by the Authors, it should be also stressed that disease duration is different between the two studies: 24 months maximum in one case [16] compared to 13 months on average in the other [21]. It might be that according to the time since the onset of the pathology, impairments in emotional memory have a different weight. Further, the absence of enhancement of memory for negative words might also be due to a mix of impairments between memory dysfunctions and valence detection deficits, as the absence of a correct attribution of valence is preliminary for this effect to manifest.

Theory of mind (ToM) and social cognition

Heterogeneity of tasks characterizes studies exploring Theory of Mind (ToM) and social cognition in ALS patients (Table 1). Two studies employed the Awareness of Social Inference Test (TASIT) [18*, 20*], two studies the Reading in the Mind’s Eye (RME) [22, 23], while the others adopted
different tests or ad hoc created paradigms. Results from the studies using the TASIT are congruent in suggesting a compromised ability to make social inferences \cite{18*, 20*}. The studies using the RME highlight diverse results: in one case patients are far away from being impaired \cite{22*}, while in the other there is a trend towards a significant impairment \cite{18*}. The only study employing the Faux Pas Test shows a general impairment in ALS patients \cite{25}. Studies that employ more than one task of ToM and social cognition show alternatively impaired or spared abilities, even within the same study \cite{19**, 22, 22, 25}. Finally, a recent voxel based morphometry (VBM) study highlights that density of grey matter is reduced in empathy related area in ALS patients: ventromedial prefrontal cortex, anterior cingulate cortex, and fronto-insular cortex bilaterally \cite{19**}.

These studies are quite congruent in highlighting a compromising of ToM, empathy, or other social abilities in ALS, backed up by differences at the neural level. The precise social component might differ across patients, possibly in relation to clinical features. Not by chance, the study showing some spared ToM abilities enrolled patients with a disease duration of 2.68 months and only 1 with bulbar onset \cite{22}, while the studies revealing impairments are based on findings from patients with on average a disease duration of 30 months \cite{20*, 23, 25} and with bulbar onset and/or concomitant cognitive impairments \cite{18*, 20*}.

**Conclusion**

Given the importance of affective processing for patients with degenerative brain disorders and their caregivers \cite{34, 35}, more recent studies also include the investigation of emotions although the anatomical regions underpinning these processes do not represent the first targets of these disease.
Nonetheless, results on emotional impairments in ALS are partially divergent. Both primary (such as recognition of facial and verbal emotional expressions) and higher (such as interpretation of others states of mind, irony or sarcasm) emotional functions have been explored.

Firstly, arousal and valence processing are both impaired in ALS, for visual and verbal modalities. This deficit seems to be associated with the impairment of the emotional memory. Secondly, FER impairments for anger, sadness and disgust, appears to be independent from cognitive dysfunction but it is unclear whether there is an association with the arousal disorder. Indeed, they are indicative of a major involvement of emotional areas within frontal rather than temporal cortices (or of the associative bundles between these structures) given the sparing of fear recognition. Results on prosody highlight that impairments emerge also for this component only if there are concomitant FER deficits, and together with findings on social cognition abilities support the hypothesis that the level of impairment for these components depends on the disease progression and severity.

Future studies should consider two main issues that possibly contribute to the non-homogeneity of the available results.

Firstly, future research would benefit from the inclusion of morphed facial expressions instead of full displays only [30*], as lowering the intensity of emotional expressions may help in revealing subtle impairments otherwise not detectable [30*]. Further, including state of the art paradigms such as those developed to explore emotional body postures recognition [36] would provide additional information on the selectivity of emotional impairments.

Secondly, a detailed clinical profile of patients is necessary, including an extensive neuropsychological assessment to control for cognitive impairments and measures of disease duration, severity and onset type, considering the continuum hypothesis between ALS and FTD and the not fully understood differences between these two clinical conditions.
Neuroimaging measures, focusing on brain atrophy as well as on connectivity, and follow up studies would be of undeniable value to this aim. The anatomical damages mainly found in the limbic system [12-14] would have suggested more focal impairments related to “temporal” emotions such as fear. An intriguing hypothesis to explain diversity in compromised components of emotion recognition and ToM abilities is that different degrees of impairment of connective bundles between areas [17**], such as the insular and frontal cortices, could explain the heterogeneity of impairments between patients and the link with other clinical manifestations. While focal damage might be more relevant for other disorders, the importance of networks connectivity (and the progression of their degeneration) in ALS appears the more and more crucial to understand differences across patients.

Conflicts of Interest and Source of Funding Acknowledgements: The Author declares no conflicts of interest. AS was supported by PRIN 2011.

Key points

- ALS is characterized by non motor impairments that have been recently shown to include emotional deficits.
- Arousal and valence detection are impaired in ALS patients independently from the stimulus modality (verbal or visual).
- Recognition of facial expressions of anger, sadness and disgust is impaired in ALS patients independently from their cognitive status.
- Type of onset (i.e. bulbar), time since onset and severity of the disease are crucial variables to understand affective impairments heterogeneity between patients.
• In ALS, emotional dysfunctions might be better explained by right hemispheric connection bundles impairments rather than by focal damages.

REFERENCES

1. Kumfor F, Piguet O. Disturbance of emotion processing in frontotemporal dementia: a synthesis of cognitive and neuroimaging findings. Neuropsychology review. 2012;22(3):280-97. This study provides a summary of emotional processing in bvFTD that can be directly compared to ALS.
This study is the first one exploring connectivity in relation to emotional processing in ALS. It is fundamental to understand why differences exists between ALS and bvFTD as it shows that fasciculi within the right hemisphere are compromised in ALS patients.
This study directly compares demented and not demented ALS patients with bvFTD patients.
This study provides the first VBM investigation in relation to social cognition in ALS patients. It shows a correlation between social abilities and right fronto-insular cortex and anterior cingular cortex grey matter providing the first evidence that emotional impairments in ALS are not a psychological reaction to the disease.
This study investigates social cognition in a large sample of ALS patients.
This study tries to replicate the first findings on emotional memory in ALS patients found in 2005.
This study provides evidence for using morphed facial expression stimuli in non demented patients.
<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>Year</th>
<th>Sample</th>
<th>DISEASE ONSET TYPE</th>
<th>MONTHS SINCE SYMPTOMS ONSET</th>
<th>ALS-FRS</th>
<th>ASSESSMENT</th>
<th>Facial Emotion Recognition Tasks</th>
<th>RESULTS</th>
<th>Other Emotional Tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crespi et al.</td>
<td>2014</td>
<td>22</td>
<td>55</td>
<td>4 bulbar</td>
<td>23.09</td>
<td>39.86</td>
<td>E&amp;F</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Savage et al.</td>
<td>2013</td>
<td>16 FTD-ALS; 13 ALS-only</td>
<td>30 healthy; 25 bvFTD</td>
<td>15 (2 in the ALS only subgroup)</td>
<td>Not specified</td>
<td>41.2; 37.3</td>
<td>E&amp;F caricature test, TASIT</td>
<td>Not specified</td>
<td>Impairment at TASIT, for FTD-ALS and bvFTD compared to controls and ALS-only</td>
</tr>
<tr>
<td>Cerami et al.</td>
<td>2013</td>
<td>20</td>
<td>56</td>
<td>4 bulbar</td>
<td>23.90</td>
<td>36.84</td>
<td>Non-verbal task of attribution of mental states to other individuals - emotional states versus intentions (graphic cartoons)</td>
<td>HADS</td>
<td>Significantly reduced performance in patients for emotion attribution; emotion attribution scores positively correlated with grey matter density in the right fronto-insular cortex and anterior cingulate cortex</td>
</tr>
<tr>
<td>Staios et al.</td>
<td>2013</td>
<td>35</td>
<td>30</td>
<td>Some bulbar (number not specified)</td>
<td>32.05</td>
<td>36.4</td>
<td>TASIT</td>
<td>HADS</td>
<td>Spared discrimination of negative and positive emotions, but impaired recognition of sarcastic and paradoxical sentences</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Patient(s)</td>
<td>Control/s/ comparison group</td>
<td>Disease Onset Type</td>
<td>Months Since Symptoms Onset</td>
<td>ALS-FRS</td>
<td>Assessment</td>
<td>RESULTS</td>
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<tr>
<td>Cuddy et al. [21]</td>
<td>2012</td>
<td>19</td>
<td>19</td>
<td>Not specified</td>
<td>13 (diagnosis not symptoms)</td>
<td>37.7</td>
<td>Brierly-Medford Sentences, Phelps Words, HADS, ELQ</td>
<td>No differences if patients analysed as a group, but impairments when considering percentage of patients scoring below 5th percentile. Differences in ratings between positive and negative words within patients.</td>
<td></td>
</tr>
<tr>
<td>Cavallo et al. [22]</td>
<td>2011</td>
<td>15</td>
<td>21</td>
<td>1 bulbar</td>
<td>2.68 (illness duration)</td>
<td>31.33</td>
<td>RME, STC, Not specified</td>
<td>Not present</td>
<td>No differences on RME; social context dimension of SCT impaired</td>
</tr>
<tr>
<td>Girardi et al. [23]</td>
<td>2011</td>
<td>19</td>
<td>20</td>
<td>Not specified</td>
<td>33.22</td>
<td>29.37</td>
<td>IGT (defined as affective decision making), HADS</td>
<td>Impaired learning at IGT</td>
<td></td>
</tr>
<tr>
<td>AUTHORS</td>
<td>Year</td>
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<td>MONTHS SINE SYMPTOMS ONSET</td>
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<td>ASSESSMENT</td>
<td>RESULTS</td>
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<tr>
<td>Girardi et al.</td>
<td>2011</td>
<td>B</td>
<td>7 bulbar</td>
<td>38.07</td>
<td>29.79</td>
<td>E&amp;F, RME, JoP</td>
<td>Impairment in inferring mental states of others (JoP); trend for RME (3 patients only outside the normal range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmieri et al.</td>
<td>2010</td>
<td>9</td>
<td>not specified</td>
<td>24 (diagnosis not symptoms)</td>
<td>37.89</td>
<td>WORDS (PLEASANT/UNPLEASANT) BDI, STAI-Y1, ELQ</td>
<td>Activation in the left hemisphere for negative words greater than in the right hemisphere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meier et al.</td>
<td>2010</td>
<td>18</td>
<td>Not specified</td>
<td>34.56</td>
<td>35.78</td>
<td>FAUX PAS TEST, PRLT, HAT, APROSODY TEST HAD</td>
<td>not present Faux pas impaired, HAT impaired at complex levels, prosody generally impaired (no differences between single emotions)</td>
<td></td>
<td></td>
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<tr>
<td>AUTHORS</td>
<td>Year</td>
<td>Sample</td>
<td>DISEASE ONSET TYPE</td>
<td>MONTHS SINCE SYMPTOMS ONSET</td>
<td>ALS-FRS</td>
<td>ASSESSMENT</td>
<td>RESULTS</td>
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<tr>
<td>Lulè et al. [26]</td>
<td>2007</td>
<td>13</td>
<td>All spinal onset</td>
<td>23 (disease duration)</td>
<td>36.8</td>
<td>IAPS</td>
<td>BDI, ALS depression index</td>
<td>Greater activation in the right supramarginal area, inferior frontal operculum, left cerebellum, and bilaterally in the primary visual cortex and inferior parietal lobe. Lower activation in bilateral higher visual areas.</td>
<td></td>
</tr>
<tr>
<td>Zimmerman et al. [27]</td>
<td>2007</td>
<td>13</td>
<td>All bulbar onset</td>
<td>Not specified</td>
<td>Not specified</td>
<td>E&amp;F, PROSODY TASK</td>
<td>GDS</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lulè et al. [15]</td>
<td>2005</td>
<td>12</td>
<td>All spinal onset</td>
<td>40</td>
<td>75.5</td>
<td>IAPS, Galvanic Skin Responses, Heart Rate</td>
<td>BDI</td>
<td>Not present</td>
<td>Patients rate stimuli as more positive, as more arousing when neutral and less when most arousing for controls, skin physiological responses different in patients, but no possibility to determine if related to single emotional components.</td>
</tr>
</tbody>
</table>
Table 1. Summary of studies exploring emotional processing in ALS. Clinical features of patients are described in the first 5 columns. Emotional assessment tests are indicated in the table to highlight commonly used instruments. Finally a summary of results is provided, separately for facial emotion recognition tasks using the Ekman & Friesen series (an X indicates that the results show an impairment in ALS patients) and for the other tests. Results always refer to ALS patients performance.

Legend:
ALS-FRS: Amyotrophic Lateral Sclerosis Functional Rating Scale (indicates both the original version and the revised version).
E&F: images taken from the Ekman & Friesen series
ALS: Amyotrophic Lateral Sclerosis; FTD-ALS: Amyotrophic Lateral Sclerosis patients with diagnosis of Frontotemporal Dementia; bvFTD: Frontotemporal Dementia behavioral variant. TASIT: The Awareness of Social Inference Test; HADS: Hospital Anxiety and Depression Scale; RME: Reading in the Mind’s Eye; SCT: Story Completion Test; IGT: Iowa Gambling Task
ELQ: Emotional Lability Questionnaire; JoP: Judgement of Preference Task; STAI-Y1: State-Trait Anxiety Inventory – Form Y; PRLT: Probabilistic Reversal Learning Test; HAT: Holiday Apartment Task; IAPS: International Affective Picture System

<table>
<thead>
<tr>
<th>Papps et al. [16]</th>
<th>2005</th>
<th>19</th>
<th>20</th>
<th>Not specified</th>
<th>Maximum 24 months</th>
<th>Not specified</th>
<th>E&amp;F, SOCIAL JUDGEMENT, SENTENCE Brierly-Medford Sentences</th>
<th>ELQ, HAD</th>
<th>o</th>
<th>o</th>
<th>o</th>
<th>ok</th>
<th>ok</th>
<th>TRENDED</th>
<th>No enhancement of memory for emotional words</th>
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</table>

No enhancement of memory for emotional words