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Dysfunctions within limbic–motor networks in amyotrophic lateral sclerosis

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ABSTRACT

Previous studies have shown that affective symptoms are part of the clinical picture in amyotrophic lateral sclerosis (ALS), the most common motor neuron disorder in elderly people. Diffuse neurodegeneration of limbic regions (e.g., prefrontal cortex [PFC], amygdala) was demonstrated in ALS *post-mortem*, although the mechanisms of emotional dysregulation in ALS *in vivo* remain unclear. Using functional imaging, we assessed the brain responses to emotional faces in 11 cognitively unimpaired ALS patients and 12 healthy controls (HCs). We tested whether regional activities and connectivity patterns in the limbic system differed between ALS patients and HCs and whether the variability in clinical measures modulated the neuroimaging data. Relative to HCs, ALS patients displayed greater activation in a series of PFC areas and altered left amygdala–PFC connectivity. Anxiety modulated the right amygdala–PFC connectivity in HCs but not in ALS patients. Reduced right premotor cortex activity and altered left amygdala–supplementary motor area connectivity were associated with longer disease duration and greater disease severity, respectively. Our findings demonstrate dysfunctions of the limbic system in ALS patients at early stages of the disease, and extend our knowledge about the interplay between emotional brain areas and the regions traditionally implicated in motor control.

1. Introduction

A growing body of research has demonstrated that the neurodegeneration underlying amyotrophic lateral sclerosis (ALS), a common motor neuron disorder associated with aging, extends to non-motor brain regions including the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), hippocampus, and amygdala (Abrahams et al., 1996; Leigh et al., 2002; Ludolph et al., 1992; Lulé et al., 2007; Lulé et al., 2010; Papps et al., 2005). The presence of neurodegenerative processes within some of these brain areas would also explain why approximately the 50% of ALS patients display, along with the typical motor deficits, a neuropsychological syndrome similar to that shown by individuals with prefrontal cortex (PFC) lesions (e.g., dysexecutive syndrome) (Lomen-Hoerth et al., 2003; Raaphorst et al., 2011; Ringholz et al., 2005; Rippon et al., 2006).

Furthermore, apathy, scarce impulse control, depression, anxiety, and personality disorders have been described in up to 60% of ALS patients, regardless of the cognitive impairment (Grossman et al., 2007; Murphy et al., 2007a, 2007b; Witgert et al., 2010). These findings indicate that emotional dysregulation may underlie the inappropriate reactions to emotional stimuli and the abnormalities in behavior and social functioning that have been described in ALS patients (Cavallo et al., 2011; Olney et al., 2011; Vignola et al., 2008; Witgert et al., 2010). In contrast, other studies have suggested that depression and anxiety may be not particularly evident in ALS patients, or, at least, would weakly correlate with disease duration and severity of motor symptoms (Bungener et al., 2005; Olsson Ozanne et al., 2011; Rabkin et al., 2005; Wicks et al., 2007). These latter findings have suggested the presence of blunted emotional responses in ALS patients who would maintain a relatively good psychosocial adjustment and a paradoxically positive approach to social situations, despite the fatal prognosis of their disease (Lulé et al., 2012).

Nonetheless, a clear model of how ALS alters the emotional brain has not yet emerged, mainly because of the paucity of studies on this topic and the presence of mixed results. Functional magnetic resonance imaging (fMRI) studies in ALS patients have indeed

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reported both enhanced and reduced responses in a series of brain regions broadly implicated in cognitive and emotional functions. In particular, ALS patients showed, relative to healthy controls (HCs), increased responses in the left middle and inferior frontal gyrus, right supramarginal area, right frontal operculum, and bilateral inferior parietal cortex while viewing affective pictures (Lulé et al., 2007). In contrast, decreased activations in the left medial frontal, right precentral, and anterior cingulate cortex (ACC) have been observed in ALS patients relative to HCs during negative priming (Goldstein et al., 2011). Furthermore, when comparing ALS patients with HCs, reduced responses to emotional pictures have been reported in extrastriate visual areas, right middle frontal gyrus, right superior parietal lobule, and right posterior cingulate cortex (Lulé et al., 2007; Palmieri et al., 2010). Finally, another study using resting state fMRI reported decreased activations in ALS patients, relative to HCs, in a series of regions of the default mode network that have been linked to cognitive as well as emotional functions (Mohammadi et al., 2009).

One way to enhance our knowledge of the pathophysiological mechanisms underlying emotional processing in ALS is to study the brain connectivity within the limbic system rather than only exploring the activity of single regions. There is evidence that the bundles of fibers linking emotional brain areas may be damaged in ALS, as assessed by diffusion tensor imaging (Canu et al., 2011; Li et al., 2012; Tsujimoto et al., 2011). In particular, ALS patients, relative to controls, displayed reduced fractional anisotropy, a measure of white matter micro-integrity, within the neuronal pathways from and to the OFC, a critical area for emotional regulation (Barbas, 1995; Davidson, 2000; Ghashghaei and Barbas, 2002; Kawasaki et al., 2005; Kober et al., 2008; Phan et al., 2002). Hence, abnormalities in the connectivity between PFC areas (e.g., DLPFC, OFC, and ACC) and regions implicated in the generation of negative emotions (i.e., amygdala) could be at the basis of emotional dysregulation in ALS. Recent research has also revealed that the interaction between the amygdala and premotor cortices represents an important mechanism by which emotions modulate motor behaviors (Pichon et al., 2008; Pouga et al., 2010). Given the extensive damage of the premotor cortices in ALS (Chang et al., 2005), it is thus possible that an abnormal interplay between the amygdala and premotor areas plays a prominent role in the manifestation of emotional symptoms in some ALS patients.

In this study, we have combined classic fMRI analyses in single regions with methods to assess the brain functional connectivity during the execution of an emotional processing task. Human faces expressing negative emotions were used as main stimuli given their strong ecological validity for probing brain networks involved in affective behaviors, particularly the PFC–amygdala circuits (Ghashghaei et al., 2007). Previous evidence has shown that ALS patients may have either unimpaired or impaired perception of emotional facial expressions as well as deficits in the judgement of the approachability of faces (Papps et al., 2005; Schmolck et al., 2007; Zimmerman et al., 2007). However, disease-related changes in the activity of brain networks underlying emotional processing cannot be revealed by neuropsychological studies. To this end, fMRI is a sensible tool to display subtle dysfunctions within limbic brain regions, even before the occurrence of noticeable behavioral abnormalities. Our study therefore addressed 3 issues: (1) whether and how the responses of single brain regions involved in emotional processing differed between ALS patients and HCs while processing emotional faces compared to neutral stimuli; (2) whether and how the functional connectivity within the limbic system (specifically the PFC and amygdala) and at the limbic–motor interface (i.e., amygdala–premotor cortex interplay) differed between ALS patients and HCs, again, as a function of viewing emotional versus neutral stimuli; (3) whether and how individual differences in anxiety and depression levels in ALS patients and HCs were related to brain regional activations and/or functional connectivity patterns.

We hypothesized that ALS significantly altered the core brain networks implicated in emotional processing and regulation. We also expected functional abnormalities at the limbic–motor interface of ALS patients relative to HCs.

2. Method

2.1. Participants

Thirteen male subjects with the diagnosis of sporadic probable/definite ALS were enrolled from the Moto Neuron Diseases outpatient Clinic of the Second University of Naples, according to the revised El Escorial criteria of the World Federation of Neurology (Brooks et al., 2000). Only patients with no mutations in the super oxidase dismutase–1 (SOD-1) gene were included, similarly to previous studies (Tedeschi et al., 2012). An expert neurologist (M.R.M.) with 20 years of experience in motor neuron disorders who was unaware of any other result assessed motor skills of ALS patients according to the Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRS-R), a 12-item scale evaluating various physical functions that can be affected by ALS (swallowing, speech, use of hands, breathing, walking, and so on) (Cedarbaum et al., 1999). Each item is rated from 0 (worst) to 4 (best), corresponding to a total score ranging from 0 to 48.

Exclusion criteria were the following: (1) fronto-temporal dementia or other forms of dementia, according to the Structured Clinical Interview of the *DSM-IV* (American Psychiatric Association, 1994); (2) history or current psychiatric disorders, according to the Structured Clinical Interview of the *DSM-IV* (the interview was administered by a trained psychotherapist (C.M.G.) and lasted approximately 1 hour) (American Psychiatric Association, 1994); (3) evidence of cognitive impairments as evaluated by a detailed neuropsychological assessment (discussed in next section); (4) history of cerebro-vascular disease, head trauma, hypertension, or diabetes; (5) assumption of psychoactive drugs, either currently or premorbidity; (6) abnormal functioning of the right upper limb that prevented the execution of the fMRI task; (7) deficit of visual acuity; (8) need of noninvasive ventilation or percutaneous endoscopic gastrostomy. All patients were taking riluzole at the time of the fMRI examination.

Twelve right-handed healthy volunteers with no previous history of neurological or psychiatric diseases and with normal MRI of the brain (as assessed by a structural MRI scanning) were matched for age and educational level to ALS patients. Demographic and clinical characteristics of all participants are summarized in Table 1.

All participants gave written informed consent, which was approved by the Ethical Committee of the University "Magna Graecia" of Catanzaro according to the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm).

2.2. Neuropsychological assessment

A trained neuropsychologist (R.M.) administered to all participants a neuropsychological battery evaluating the following functions: (1) verbal and spatial memory (Rey Auditory-Verbal Learning Test [RAVLT]), Immediate and Delayed Recall (Rey, 1958); (2) executive functions and cognitive flexibility (Modified Card Sorting Test) (Nelson, 1976); (3) verbal fluency (Controlled Oral Word Association Test [COWAT]) (Benton et al., 1994); (4) visuo-spatial skills (Benton et al., 1978); (5) anxiety and depression levels (Hamilton Rating Scale—Anxiety (HAM-a), Hamilton Rating Scale—Depression