Evoked cardiac response components in cognitive processing: differential effects of amyotrophic lateral sclerosis

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Abstract. We investigated the mechanism of two evoked cardiac response components associated with different aspects of information processing. Innocuous stimuli presented in an irrelevant condition elicit a simple cardiac deceleration termed ECR1. The same stimuli presented in a relevant condition (such as results from requesting subjects to silently count the stimuli) elicit a complex biphasic response with a large secondary acceleration in heart rate. This difference is attributed to the additional effect of cognitive task performance, resulting in an addition response component, ECR2. This may be realised by subtraction of the two responses. We investigated the mechanisms involved by comparing cardiac response profiles from a neurologically-impaired group with those from a control group. amyotrophic lateral sclerosis (ALS) has been associated with a loss of synaptic connections in the frontal lobe. Twelve ALS clinically non-demented patients were age-matched with twelve neurological patients without pathological changes in the brain. Cardiac response profiles for ECR1 and ECR2 were examined as a function of group. ECR1 did not differ between the groups, but ECR2 was significantly impaired in the ALS patients. The results are discussed in terms of different brain regions associated with these two cardiac response components. ECR1 may be associated with automatic preattentive stimulus registration involving, in the case of auditory stimuli, the auditory analyser and associated pathways, while ECR2 appears to be a correlate of controlled executive processing, involving the frontal cortex.

The commonly-observed response fractionation of measures of the orienting response (OR) is interpreted in terms of different processing stages separately determining the different physiological responses. Preliminary Process Theory (Barry 1996) regards the multi-component OR as a reflection of the sequence of processing stages involved in elaboration of the stimulus characteristics.

Among OR measures the evoked cardiac response (ECR) deserves special attention because it shows two different time-courses, which appear under different circumstances. The ECR elicited by an innocuous stimulus when no experimental task requirements are imposed upon the subject (which means an irrelevant stimulus if it is innocuous in intensity) most often is a simple early deceleration of the heart rate (HR). The cardiac cycle in which the stimulus onset occurs and the subsequent cardiac cycle are reflexively slowed - a primary bradycardia (Lacey and Lacey 1980). These two slower heart beats can be followed by a return towards baseline or the deceleration of HR may be prolonged for several seconds before HR reaches the baseline level again. The former reflects the pure effect of stimulus registration. The latter can be associated with an additional continuation of perceptual stimulus processing. This initial obligatory evoked HR deceleration is referred to as ECR1 - marking an early automatic phase of stimulus processing (Barry 1983, 1996).

Increased stimulus significance, such as may be generated by instructions to respond to the stimulus in some way (e.g. to count the stimuli) and hence producing a relevant stimulus, generates a largely acceleratory HR response, usually with some initial deceleration related to ECR1. The acceleration of HR evoked in the relevant condition, which reflects an effect of mental task performance (such as we use in our experimental paradigm), is only observed in combination with the obligatory ECR1. Thus some form of subtraction of responses (ECR1 evoked by the irrelevant stimulus from ECR1+ECR2 evoked by the relevant stimulus) is necessary to estimated ECR 2, the later component of the complex ECR (Barry and Tremayne 1987, Barry 1996).

Basically, ECR1 and ECR2 were hypothesised, on the basis of inferences from the effects of manipulation of psychological factors (stimulation, instruction), to be two independent responses separately determined by different neurophysiological processing stages (Barry 1987). This conceptualisation requires confirmation on the basis of some differentiation of the brain mechanisms

which participate in the output display of ECR1 and ECR2. Of these two cardiac response components, the latter seems to be related to higher-level executive functions of the brain. If so, a selective impairment of a brain mechanism involved in executive functioning should attenuate the time-course of ECR2 but not necessarily ECR1.

amyotrophic lateral sclerosis (ALS) is usually described as a motoneuron disease which impairs executive behaviour but spares cognitive function. However, recent publication have reported cognitive impairment associated with ALS (Abrahams et al. 1996, Massman et al. 1996, Abe et al. 1997, Abrahams et al. 1997). The data have suggested the presence of a continuum of cognitive disability in patients with ALS, corresponding to the pathological process in the frontal lobe, and ranging from normality to significant impairment. Other data suggest that executive frontal lobe functions are not spared in ALS but in some cases this impairment is subtle (Dary-Auriol et al. 1997). Among major symptoms of frontal lobe damage are impairments of temporal memory, recency memory, self-order recall, and delayed response (Kolb and Whishaw 1990), and some of these symptoms are apparent in ALS. The above-mentioned data indicate that the consequences of ALS are not limited to a mere loss of peripheral muscular ability, but that the selective degeneration of motoneurones causes dysfunction of the central executive mechanisms of the brain.

Studies of cortical function in ALS have shown a significant reduction of regional cerebral blood flow (rCBF), principally in areas of the frontal lobe - in the lateral premotor area and the supplementary motor area (Kew et al. 1993a). Another study of ALS patients showed significantly attenuated rCBF in some areas of prefrontal cortex during performance of a motor task (Kew et al. 1993b). It is assumed that rCBF reflects synaptic activity and therefore that the abnormalities of rCBF in the cortical areas of ALS patients reflects at least a partial loss of synaptic connections.

There is no evidence that cortical areas such as the occipital and temporal cortex, which neither receive projections from motor or premotor areas nor project through the corticospinal tract (Jones and Powell 1970, Pandya and Vignolo 1971), show significantly reduced rCBF in ALS patients. It suggests that synaptic connections in these regions of the brain remain normal.

On the basis of the assumption that the prefrontal cortex and cortical motor system and associated areas are in-

volved in tacit mental performance in the intact brain, and the existence of covariation of HR and motor system activities, we predicted that ALS would cause an impairment of the regular pattern of the accelerative component of the ECR, ECR2, which has been identified as a correlate of mental performance. We did not predict an impairment of the pattern of the decelarative component of the ECR, ECR1, with ALS.

Twelve clinically non-demented ALS patients (6 males and 6 females, 37-68 years old) and twelve controls (4 males and 8 females, 37-68 years old) were used as subjects. Patients with ALS were selected according to WFN criteria (Brooks et al. 1994). The subjects in the control group were suffering from headache or dizziness diagnosed as a tension-like headache, migraine or vertebrobasilar insufficiency without any pathological changes in the brain evidenced by CT or MRI examination. All ALS patients showed evident symptoms of upper motor neurone (pyramidal) lesions.

HR and respiration were recorded with S&W standard electrodes connected to an S&W electrocardiographic and respiration device. The output from an R-wave peak detector was used to compute R-R intervals with 50 ms resolution. Measures of HR were calculated as mean values in 0.5 s intervals for 30 s epochs, starting 20 s before each stimulus. Corresponding values of respiratory activity were obtained and used in off-line analyses to correct HR for respiratory sinus arhythmia, which clarifies the shape of the ECR by reducing its variability (Barry et al. 1992).

Each session lasted 30 minutes. Subjects were seated in a comfortable armchair in an air conditioned electrically shielded, sound-isolated chamber which was separated from the recording equipment.

Subjects received 10 innocuous auditory stimuli (60 dB, 1,000 Hz, 1 s duration, 20 ms rise and fall times), with interstimulus intervals randomly varying between 40 and 60 s. Stimuli were presented in one of two conditions. In the first condition subjects were told there was no task related to the sounds they would hear (irrelevant condition), while in the second condition they were requested to silently count the number of stimuli to later report to the experimenter (relevant condition).

For the present purpose, the complex ECR was defined by the 11 time points just after the stimulus onset, relative to the immediately-prestimulus value of HR.

Figure 1 shows the average ECR1 profiles obtained for both groups in the irrelevant condition. A simple de-

celeration in HR is apparent as the response of both the ALS and control group. These response profiles were compared using a two-way repeated measures ANOVA with the between-subjects factor of group and the within-subject factor of time (12 points). Within the time factor, linear, quadratic and cubic trends were examined. Such single degree of freedom F-tests avoid the problems of non-sphericity of the variance-covariance matrix often found with repeated-measures analyses of autonomic data. The response form was evident in significant quadratic ($F_{1,22} = 5.13$, $P=0.034$) and cubic ($F_{1,22} = 19.46$, $P=0.001$) trends over time. Although it appears that the ALS group had a prolonged cardiac deceleration than the control group, there was no significant group effect or group x time interaction. That is, there was a significant deceleratory response, ECR1, which did not differ between the groups.

All subjects from both the control and ALS groups reported the correct total number of stimuli presented in the relevant condition. Figure 2 shows the average ECR profiles obtained for both groups in the relevant condition. Both groups showed an initial deceleration in HR, followed by a rapid acceleration in the control group which was not apparent in the ALS group. A similar ANOVA to that above indicated that, over the two groups, the mean response form was apparent in significant linear ($F_{1,22} = 5.77$, $P=0.025$), and cubic ($F_{1,2\,2}= 39.56$, $P=0.001$) trends over time. There was a significant group x time interaction in relation to the quadratic trend over time ($F_{1,22} = 5.55$, $P=0.028$), and a significant
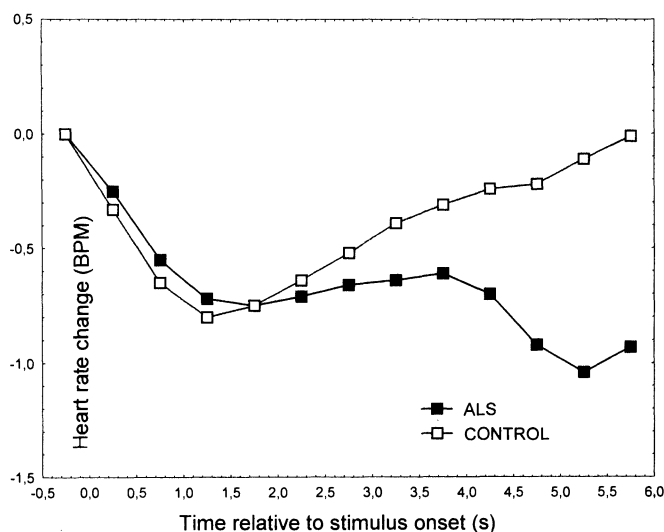

Fig. 1. The average ECR1 profiles obtained for both groups in the irrelevant condition.

overall group difference in mean HR ($F_{1,22}$ = 4.64, P=0.042). That is, in the relevant condition, the control group showed the expected biphasic response form while the ALS showed only a deceleration in HR.

The response profiles for ECR2 shown in Fig. 3 were derived by subtracting the ECR1s of the irrelevant condition (Fig. 1) from the complex ECRs of the relevant condition (Fig. 2). The expected largely-accelerative ECR2 is readily apparent for the control group, but not for the ALS group, which shows a small, gradual acceleration, which peaks approximately 2.5 s later. These response profiles were examined using a three-way repeated measures ANOVA with the between-subject factors of group and instruction (relevant *versus* irrelevant), plus the within-subject factor of time (including simple trends). In this analysis, ECR2 effects (i.e., the difference between responses in the relevant and irrelevant conditions) correspond to the statistical effects or interactions involving instruction. Figure 3 shows that is due to the difference in HR acceleration (ECR2) evoked in the relevant condition. Averaged across groups, there was a significant interaction between instruction and the linear trend over time points ($F_{1,22}$ = 4.81, P=0.039). This indicates that the mean of the ECR2 responses shown in Fig. 3 includes a linear increase in HR over the epoch. There was also a significant three-way interaction between group, instruction and the quadratic trend over time points ($F_{1,22}$ = 6.39, P=0.02). This means that the ECR2 profiles of the two groups differ in their quadratic
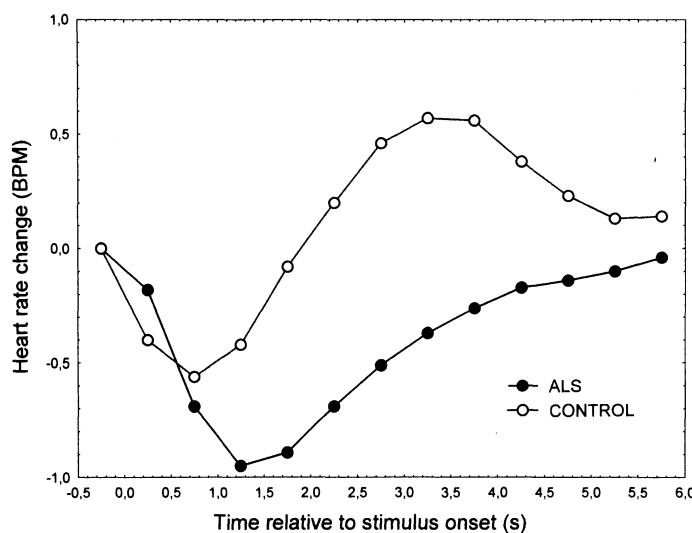
trend over time points. That is, the ALS patients show an ECR2 component in the relevant condition which is significantly reduced and different in shape from that of the control group.

As shown in Fig. 1 and confirmed in the statistical analysis, ECR1 evoked by innocuous auditory stimuli in an irrelevant condition did not differ between the groups in terms of either magnitude or timing. Considering ECR1 as a correlate of stimulus registration, an early component of stimulus processing, this result indicates that the brain structures underlying this early perceptual process are intact in ALS patients. Our data are consistent with the rCBF studies, described above, which showed no reduction in blood flow in the temporal cortex of ALS patients, indicating that synaptic connections in this region remain normal. This cortical normality appears to allow ALS patients to carry out at least some automatic early processing of auditory stimuli, comparable with the performance of the control subjects.

The complex cardiac response profiles obtained in the relevant condition (see Fig. 2) showed a similar initial deceleration during the first second. The control group then exhibited cardiac acceleration, an effect not apparent in the ALS patients. Rather, the ALS response continued to decelerate for another 0.5 s. before beginning to return to baseline. This significant difference suggests that the accelerative ECR2 component of the complex response is significantly impaired in ALS patients compared with the control group.

In order to explore this difference in more detail, we derived ECR2 by subtraction, as shown in Fig. 3. Statistical analysis confirmed that these response profiles differed significantly, with the ECR2 of the ALS patients differing in both size and shape. That is, although the ALS patients were able to correctly perform the task, the evoked cardiac response component associated with this task performance was substantially diminished.

Figure 3 can be interpreted as showing a smaller and slower ECR2 in ALS patients, which, if there is a strong link between cognitive load and ECR2, might suggest some loss of cognitive functioning. This was not apparent in performance on our simple task, but might be apparent in other tasks. If so, the magnitude of the ECR2 cardiac response may serve as an indicator of subtle cognitive dysfunction. Alternatively, if we consider that the cognitive function of our ALS patients has been spared, at least at the level of our simple counting task, perhaps the covariation of HR and mental performance has been weakened. The cortical motor system which, in the intact

Fig. 2. The average ECR profiles obtained for both groups in the relevant condition.
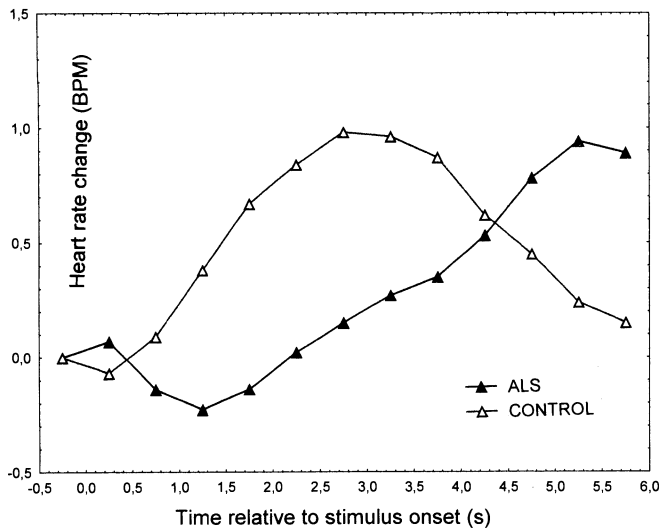
Fig. 3. The response profiles for ECR2 derived by subtracting the ECR1s of the irrelevant condition (Fig. 1) from the complex ECRs of the relevant condition (Fig. 2).

brain, is engaged in tacit mental performance, may not be a crucial component of that performance, but play a role as a link between tacit mental performance and changes in heart rate.

Although it is not possible to choose between these alternatives on the basis of our current knowledge, it is readily apparent that these data demonstrate the involvement of separate mechanisms in the elaboration of ECR1 and ECR2.

As discussed above, rCBF studies indicate that synaptic connections in the temporal cortex and its associated pathways remain normal in ALS patients. This suggests that the automatic early processing of auditory stimuli, the coding of the stimulus transient associated with generation of the ECR1 component, involves a pathway to the temporal cortex. That is, we propose that the auditory ECR1 is generated within the auditory analyzer, which neither receives projections from motor or premotor areas nor projects through the corticospinal tract, and hence is not affected by the motoneurone degeneration of ALS.

Clearly, the mechanism underlying ECR2 is different from that of the ECR1 component, as the form of the response decreases with the selective neuronal degeneration of ALS. This is limited to the frontal cortex and associated pathways, and hence these structures must be involved in generation of the ECR2 component. The frontal cortex has traditionally been associated with executive functioning, and hence these data support the

identification of ECR2 as a correlate of some aspects of executive functioning.

Thus we can distinguish two separate components, ECR1 and ECR2, in the complex cardiac response evoked in situations involving the cognitive processing of a simple innocuous stimulus. Each of these corresponds to different cognitive functions of the brain - automatic preattentive stimulus registration (ECR1) and controlled executive processing (ECR2) - which originate in different brain structures.

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