A functional MRI study of motor dysfunction in Friedreich's Ataxia

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Purpose

Friedreich's ataxia (FRDA) is the most common form of hereditary ataxia. The aim of the study was to examine dysfunction in motor-related areas involved in the execution of increasingly complex finger tapping tasks in individuals with FRDA. Specifically, we aimed to investigate the changes in blood oxygenation level dependent (BOLD) signal in the cerebellum, putamen, parietal and frontal lobes during the motor tasks. We hypothesized that individuals with FRDA would differentially activate these brain regions compared with controls and that functional re-organization of the cortico-cerebellar, cortico-striatal and parieto-frontal loops would occur as the result of pathology in the cerebellum.
Methods and Materials

Thirteen FRDA and fourteen controls participated. Functional MRI images were acquired during finger tapping tasks consisting of regular and irregular visually cued tasks, a self-paced task and a visually-cued multi-finger task.

Task

During the regular single finger tapping task, only one finger was required to be tapped repeatedly at a rate of 0.66 Hz. In the irregular single finger tapping task, participants were guided to maintain tapping of one finger at three different inter-tap intervals (500, 1750 and 2500 ms), pseudorandomly distributed, with a mean frequency of 0.66 Hz. Participants were asked to tap their fingers according to a visually-cued pseudorandom spatial sequence at a rate of 0.66 Hz in the regular multi-finger tapping task. Finally, in the self-paced finger tapping task, participants were instructed to maintain a self-paced finger tapping at a rate of 0.66 Hz. During the rest periods, an image of the right hand without a green circle was shown, and participants were requested to remain relaxed without making any response.

Image acquisition

Functional imaging acquisition was performed with a Siemens TrioTim 3T scanner located at Royal Children's Hospital, Melbourne, Australia, using an eight channel standard head coil.

Echo planar functional brain images were acquired using BOLD contrast (time echo: 40 ms, time repetition: 3,000 ms, in-plane resolution: 1.64 mm × 1.64 mm, slice thickness: 4.2 mm).

Image analysis:

FEAT version 5.98 (FSL, www.fmrib.ox.ac.uk/fsl) was used for all pre-processing steps and data analysis.

Based on the mean group activation maps, four regions of interest (ROI) were selected for further investigation of the BOLD signal time-series differences between groups.

1. left primary motor cortex (conjunction mask of the activated left primary motor cortex region in all subjects)
2. left basal ganglia (MNI mask of the putamen)
3. left supplementary motor area (SMA) (conjunction mask of the activated area in the left supplementary motor area region) and right inferior parietal
area (conjunction mask of the activated area in the right inferior parietal lobule) with this mask called the fronto-parietal loop

4. right V and VI lobule of the cerebellum (conjunction mask of activated motor-related cortex of the right cerebellum in the controls in all four finger-tapping tasks)

The ROI BOLD signal values for each finger tapping task were then extracted. The extracted data were analysed in SPSS version 15 (SPSS Inc., Chicago, IL). Repeated-measures ANOVA was performed to investigate between group differences in the BOLD signal temporal characteristics of each ROI during each finger tapping task.
Results

Both groups showed significant activation of the motor network (Fig 1). During the regular visually cued task, the right hemisphere of the cerebellar cortex, bilateral supplementary motor areas and right inferior parietal cortex showed higher activation in controls, whilst in FRDA the left premotor cortex, left somatosensory cortex and left inferior parietal cortex were more active. During the irregular visually cued task, the right middle temporal gyrus in controls and the right superior parietal lobule and left superior and middle temporal gyri in FRDA showed higher activation. During multi-finger task, controls showed higher activation in the middle frontal gyri, somatosensory cortices, inferior parietal lobules bilaterally and left premotor cortex, left supplementary area, right superior frontal gyrus and right cerebellum, while FRDA showed increased activity in the left inferior parietal lobule, left primary motor cortex, left middle occipital gyrus, right somatosensory cortex and the left cerebellum. Only the right crusI/II of the cerebellum showed higher activation in FRDA during the self-paced task, whereas widespread regions including the left superior frontal gyrus, left central opercular cortex, left somatosensory cortex, left putamen, right cerebellum, bilateral primary motor cortices, bilateral inferior parietal lobules and the left insula were more active in controls (Fig 2).

The right angular gyrus showed significantly higher activation in the individuals with FRDA as the result of the irregularity of single finger tapping. The effect of internally generating rhythm resulted in significantly higher activity in the right PMd, bilateral LPi; SMA/CMA; putamen and somatosensory cortex, right paracingulate gyrus, right insula and left crus I and lobule VI of the cerebellum in the controls in comparison with the individuals with FRDA. The effect of multi-finger random finger tapping showed increased activity of the left occipital fusiform gyrus and left crus I of the cerebellum in the individuals with FRDA in comparison with the controls, while several areas including the bilateral superior and inferior parietal lobules, bilateral somatosensory cortices, right middle temporal gyrus and right lobule V of the cerebellum were significantly more activated in controls than in the individuals with FRDA (Fig 3).

In both groups, the fluctuation of the primary motor cortex BOLD signal during the finger tapping task showed a similar pattern in all finger tapping tasks (Fig 4a). Although the pattern of the BOLD signal from the putamen was different during the self-paced regular finger tapping task to the other tasks in controls, in individuals with FRDA there was no distinction of the signal between the tasks (Fig 4b).

Activation in the SMA in all four tasks was significantly higher in controls in comparison with the individuals with FRDA (one-way ANOVA, corrected for multiple comparison; \([F_{\text{regular single finger}} (1, 286) = 18.95, p < 0.001]\), \([F_{\text{irregular single finger}} (1, 190) = 17.59, p < 0.001]\), \([F_{\text{regular multi-finger}} (1, 190) = 15.89, p < 0.001]\) and \([F_{\text{self-paced}} (1, 190) = 23.72, p\).
In the irregular single finger tapping and self-paced finger tapping tasks, right LPi activation was significantly greater in the controls in comparison with the individuals with FRDA (one-way ANOVA, corrected for multiple comparison; \( F_{\text{irregular single finger}} (1, 190) = 7.77, p < 0.001 \) and \( F_{\text{self-paced}} (1, 190) = 5.06, p < 0.001 \)) (fig 4c).

In the controls, the percentage BOLD signal change of the cerebellum was significantly greater during the irregular single finger tapping task \( (p=0.016) \) and regular multi-finger tapping task \( (p=0.022) \) tasks compared with during the regular single finger tapping task. By comparison, in the individuals with FRDA, the percentage of BOLD signal change was not different amongst the finger tapping tasks (fig 4d).
Fig. 1: Brain activation during the regular single finger tapping task. Red indicates brain areas with significantly higher activation in controls compared with individuals with FRDA. Blues indicates areas with significantly higher activity in individuals with FRDA compared with controls (Z>2.3, pcorrected)

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**Fig. 2:** Activation maps during the four different finger tapping tasks: (a) regular single finger tapping task, (b) irregular single finger tapping task, (c) regular multi-finger tapping task and (d) self-paced finger tapping task. Red indicates brain areas with significantly higher activation in controls compared with individuals with FRDA. Blues indicates areas with significantly higher activation in individuals with FRDA compared with controls (Z>2.3, pcorrected)

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**Fig. 3:** Brain activation as the result of (a) irregularity (irregular single finger-regular single finger) (b) un-predicted finger (regular multi-finger-regular single finger) and (c) internal generating rhythm (self-paced-regular single finger). Red indicates areas with significantly higher activity in controls compared with individuals with FRDA, and blue indicates areas with significantly higher activity in individuals with FRDA compared with controls.

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Fig. 4: (a) Percentage BOLD signal change in left primary motor cortex for controls (shown in green) and for individuals with FRDA (blue) during the regular single finger tapping task (shaded area between 9 to 36 secs); (b) BOLD signal time-series of the left putamen. The BOLD signal of the putamen during the regular single finger, irregular single finger and regular multi-finger tapping tasks was significantly different between the two groups (P-value=0.004, P-value

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Conclusion

1. Brain regions known to be commonly activated in motor tasks (primary motor cortex, SMA, PMv and PMd, somatosensory cortex and the cerebellum) were activated in both groups [1].

2. We found that the intensity of the BOLD signal in the individuals with FRDA was marginally higher in comparison with the controls, suggesting that motor movements in individuals with FRDA may be more dependent on activity in primary motor cortex than in other brain regions, perhaps to compensate for abnormal input from the cerebellum.

3. In individuals with FRDA, the BOLD signal changes of the putamen were identical during all four finger tapping tasks, which may be a consequence of cerebellar dysfunction and as was shown by Ginestroni and co-workers [2] is correlated with disease severity.

4. SMA activity was significantly lower in individuals with FRDA in all four finger tapping tasks than it was in controls, suggesting a lack of corrective input from the SMA into the motor cortex in generating accurate motor responses [3]. Only during the regular multi-finger tapping task, which requires more attention with respect to tapping a predetermined finger, did activation of the right LPi reach the same level in individuals with FRDA as in controls. This suggests that in individuals with FRDA the regular multi-finger tapping task invoked a compensatory mechanism for the cerebellar deficiency, also indicated by their low error rate for this task.

5. We showed that in healthy subjects, the cerebellar BOLD signal increased with increased task complexity, suggesting that greater cerebellar activity is required to maintain accurate complex motor performance. Individuals with FRDA lacked this adaptive and compensatory mechanism, showing similar cerebellar activity regardless of the complexity of the motor task (fig 5).
Fig. 5: Schematic diagram of the connections in the cortico-striatal and cortico-cerebellar loops. The cortico-striatal loop (left side) includes projections from the motor cortex and frontal lobe to the putamen which then projects via the GPi and the thalamus (ventrolateral/ventroanterior nuclei) back to the motor cortex. The cortico-cerebellar loop (right side) includes projections from the motor cortex and parietal lobe to the dentate nucleus via the pontine nucleus, and projections back to the motor cortex via the thalamus (ventrolateral nucleus). (GPi: internal globus pallidus). The indirect cortico-striatal pathway, which is inhibitory at the level of the thalamus, is not shown.

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References