The functional significance of perinatal corpus callosum damage: an fMRI study in young adults

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Summary
We used functional MRI (fMRI) to establish the functional significance of corpus callosum damage in young adults who had been born very preterm. Seven subjects from a cohort of individuals who had been born at <33 weeks gestation and who had sustained callosal damage visualized on structural MRI were compared while they carried out auditory and visual tasks requiring callosal transfer with nine very preterm subjects with corpora callosa of normal appearance on structural MRI, and with seven full-term controls. The very preterm subjects with damaged corpora callosa had significantly different activation patterns compared with the two control groups. In the visual task, additional activity was seen in the right dorsolateral prefrontal cortex of the damaged callosum group, possibly because the task was accomplished by storing information in working memory. On the auditory task, a deficit of activity was seen in the right temporal lobe of the callosum group. The findings reveal a plasticity of function compensating for early damage to the corpus callosum.

Keywords: corpus callosum; cerebral plasticity; periventricular haemorrhage; preterm birth; fMRI

Introduction
Although the mortality rate among preterm and low birth weight infants has fallen sharply since the introduction of neonatal intensive care (Nishida, 1993; Battin et al., 1998; Richardson et al., 1998), little is known about the effects of preterm birth for long-term neuropsychological function.

We previously have reported the results of structural MRI examination of the brains of 72 adolescents who had been born before 33 weeks of gestation (Stewart et al., 1999). The most common focal structural abnormality in these individuals was thinning/atrophy of the corpus callosum, particularly posteriorly, which was noted in 43% of preterm individuals but in only 14% of age- and sex-matched controls who had been born at full term. The corpus callosum is known to be especially vulnerable to adverse consequences of premature birth such as ischaemia, haemorrhage and sepsis, because of its longer myelogenetic cycle (Valk and Njiokiktjien, 1991) and also because of its position adjacent to the periventricular region, one of the most common sites for haemorrhage in the preterm infant (Thorburn et al., 1981; Fawer et al., 1984).

These abnormalities of the corpus callosum may have functional significance. For example, follow-up studies of preterm infants have indicated that callosal abnormalities underlie poor performance on the Kaufman Assessment Battery for Children (K-ABC) (Kaufman and Kaufman, 1983), and on the simultaneous processing scale and performance subscale of the WISC-R (Wechsler, 1974) at age eight (Roth et al., 1993). In adolescence, preterm individuals have more neurological, adjustment and reading impairments than controls born at term (Stewart et al., 1999) and have poorer educational outcome (Botting et al., 1998).

In order to investigate the functional consequences of the corpus callosum abnormalities, we examined the performance of preterm-born young adult males with corpus callosal damage, preterm-born young adult males without corpus callosum damage and term-born controls on visual and auditory tasks requiring callosal transfer during functional MRI (fMRI). The two sensory modalities allowed us to examine different portions of the corpus callosum. Visual fibres are carried in the splenium of the corpus callosum, and auditory fibres in the posterior third of the body of the corpus callosum (Berlucchi and Aglioti, 1999). Our strategy was to compare brain activity during the performance of two tasks within each sensory modality, one of which required the callosal transfer of information and the other of which did not, and to examine differences in the pattern of activation between the three participant groups. While the tasks themselves may have non-callosal components, their design ensured that callosal transfer facilitated successful completion of the task. In the visual domain, we compared the activity related to a bilateral task in which stimuli were...
presented across the vertical meridian with a unilateral task in which stimuli were presented in one hemi-field. In the bilateral task, each shape is presented to a different hemisphere, the one in the right visual field to the left hemisphere and the one in the left visual field to the right hemisphere. Agenesis of the corpus callosum leads to a performance deficit in this task, suggesting that its normal completion requires a callosal transfer (Karnath et al., 1991). For the unilateral task, visual callosal transfer is not required since both shapes are presented to a single hemisphere.

In the auditory domain, we compared the activity related to a timbre discrimination task presented to the left or right ear. The rationale for this approach relates to the findings that (i) monaural stimulation activates predominantly the contralateral hemisphere through subcortical pathways (Woldorff et al., 1999) and (ii) timbre discrimination is processed in the right hemisphere (Sidtis, 1980; Samson and Zatorre, 1994; Platel et al., 1997). We hypothesized that auditory stimuli presented to the left ear would cross subcortically to the right hemisphere and undergo timbre discrimination processing without callosal transfer. In contrast, auditory stimuli presented to the right ear would cross subcortically to the left hemisphere, and then require a callosal transfer back to the right hemisphere for timbre discrimination processing.

We predicted that the group with callosal thinning would have poorer performance on the bilateral visual task and the right ear auditory task, compared with the unilateral visual and left ear auditory tasks, and that this would be reflected in a different cortical activation pattern compared with the preterm controls with normal callosal appearance and term-born controls. We also predicted that we would not find any differences between the group of term-born controls and the preterm normal callosal group. The pattern of group-specific differences would help elucidate the neurobiological mechanisms compensating for perinatal damage to the corpus callosum.

Methods
Subjects were recruited from a cohort of infants who had been born before 33 weeks gestation and admitted to University College Hospital London Neonatal Unit between 1979 and 1980. These individuals became part of a longitudinal study of development, and underwent structural MRI scanning at age 14 or 15 years (Stewart et al., 1999) and the scans were rated independently by two neuroradiologists. From the radiologists’ reports, those scans showing thinning or atrophy of the corpus callosum and no other focal brain abnormalities were identified (i.e. no severe generalized or lobar atrophy, CSF shunts or other focal damage). From these subjects, seven male right-handed individuals between the ages of 18 and 20 years were invited to take part in the study. A further group of nine right-hand individuals from the cohort whose MRI scan was reported normal and without callosal thinning at age 14 or 15 years were also recruited, together with a group of seven right-handed age-matched subjects who had been born at full term.

Handedness was assessed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects also completed a National Adult Reading Test (NART) (Nelson, 1982). Handedness data for one of the subjects in the preterm control group, and NART data for one of the subjects in the term controls were not available. All subjects included had: (i) no contraindications to MRI; (ii) vision unimpaired without glasses; (iii) no difficulties in hearing; (iv) no neurological illness; or (v) no history of substance misuse. All subjects gave written informed consent and the study was approved by the ethical committee of The Bethlem and Maudsley Hospital.

Experiment 1: visual paradigm
Subjects were instructed to focus on a central crosswire on a projection screen throughout the experiment. Stimuli were black outlines of geometric shapes (square, rectangle, rhomboid) projected tachistoscopically onto a screen with an exposure time of 150 ms and subtending a visual angle of 1°. Subjects were instructed to respond as to whether pairs of shapes were the ‘same’ or ‘different’, using a button press with their right hand.

Pairs of shapes were presented in blocks of six in 30 s scanning epochs under the following conditions: (i) bilaterally, 4° to either side of the central crosswire; (ii) unilaterally, one located centrally 1° below the crosswire and the other 4° to the left of the central crosswire; and (iii) centrally, 1° above and 1° below the crosswire (Fig. 1). The central stimulus was included as part of a separate study to investigate the bilateral field advantage and will not be discussed further here (Santhouse et al., 2002).

Each block was presented four times in a pseudorandom order during the 6 min fMRI experiment so that a total of 72 pairs of stimuli were seen altogether in the 12 blocks. Response times were measured from the onset of presentation of the stimuli, and a log was kept of response accuracy. Subjects practised the paradigm for 6 min before they entered the scanner.
Experiment 2: auditory paradigm

Subjects were asked to close their eyes and judge as to whether pairs of sounds were the ‘same’ or ‘different’. Stimuli were notes at 440 Hz, generated using Cool Edit 96 (Syntrillium Software Corporation, Ariz., USA) which differed only in their timbre (Fig. 2). Each sound lasted for 750 ms and was separated from its paired sound by a gap of 1000 ms.

The stimuli were presented in blocks of five in 30 s scanning epochs under the following conditions: (i) presented to the right ear; and (ii) presented to the left ear. Each block was presented alternately five times throughout the 5 min experiment, a total of 50 comparisons over the course of 5 min. Response times were measured from the onset of presentation of the stimuli, and response accuracy was measured. Subjects performed the experiment (i) with the button press in their left hand and (ii) with the button press in their right hand. Subjects practised the paradigm for 5 min before entering the scanner.

Fig. 2 The sound stimuli consisted of the fundamental frequency of 440 Hz plus the first two harmonics (top); the fundamental frequency and three harmonics (middle); or the fundamental frequency and four harmonics (bottom).
Analyses

Behavioural data

The data were analysed by means of SPSS for Windows (version 8.0.2). For accuracy data, a single score of the percentage of correct responses was included for each subject. Separate analyses were conducted on accuracy and response times. For visual experiments, a two-way repeated measures analysis of variance (ANOVA) was carried out with field (bilateral and unilateral) as a within-subject factor and group as a between-subject factor, with three levels (term controls, preterm controls and damaged corpus callosum).

For auditory experiments, three-way repeated measures ANOVAs were performed, with two within-subject factors (ear and hand) each with two levels (left or right); and one between-subject factor, group, with three levels. Multivariate statistics were used to test significance.

Imaging

Scan parameters

Functional images were acquired on a 1.5 T GE Neuro-optimized Signa LX Horizon System (General Electric, Milwaukee, Wisc., USA), using a gradient echo planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (TR, repetition time = 3 s; TE, echo time = 40 ms; flip angle 90°; 64 × 64 matrix; in-plane voxel size 3.75 × 3.75 mm) and 20 axial slices, 7 mm thick with a 0.7 mm interslice gap.
Image analysis

Structural images. High resolution sagittal images were acquired for all of the term control group, five of the preterm control group and five of the damaged corpus callosum group. Data for the other subjects were unavailable. For each group, the images were normalized using SPM99 (http://www.fil.ion.ucl.ac.uk/spm) and a mean image generated, to help localization of activation maxima. The normalized structural image from each subject was segmented into white matter, grey matter and CSF images.

Functional images. Auditory and visual experiments were analysed separately. For each subject, the time series was motion corrected (Friston et al., 1996), transformed into standard stereotaxic space (Talairach and Tournoux, 1988) smoothed with a 10 mm FWHM (full width half maximum) Gaussian filter and high pass filtered using SPM99. Covariates were modelled with a boxcar convolved with the haemodynamic response function.

Statistical inferences

In order to compare the generic activations associated with each of the three groups, a two-stage random effects analysis was used for each hypothesis tested (Friston et al., 1999). The first stage generated subject-specific contrast images from the weighted linear sum of covariate parameter estimates. For the visual task, the contrast images were for bilateral versus the unilateral stimulation, while for the auditory task the contrast images were for left ear versus right ear stimulation. The second stage assessed the differences in generic activations for each group with pairwise t test comparisons: term controls versus damaged callosum group; term controls versus preterm controls; and damaged callosum group versus preterm controls. Within-group comparisons were made for the visual and auditory tasks for each of the subject groups using a fixed effects model, to show activations in the groups separately.

For the structural comparisons, separate ANOVAs were generated for white matter, grey matter and CSF images. All random effects structural and functional statistical parametric maps were thresholded at P < 0.01, corrected for multiple comparisons at the cluster level. Within-group fixed effects models were thresholded at P < 0.001, corrected for multiple comparisons at the cluster level.

Results

There was no significant difference in handedness between the full-term controls, preterm controls and damaged callosum group. Mean laterality quotient scores on the Edinburgh Handedness Scale were, respectively, 89.7 (SD 12.2), 89.1 (SD 13.8) and 76.3 (SD 28.7) [F(2,19) = 1.08, P = 0.358]. There were no significance differences in intelligence in the three groups, as measured by the NART. Mean IQ scores for the three groups were, respectively, for the full-term controls, preterm controls and damaged callosum group 114 (SD 4), 109 (SD 9.5) and 104 (SD 10.7) [F(2,19) = 2.16, P = 0.14].

Structural image comparisons

Statistical comparison of the white matter images in the damaged callosum group and control groups showed a significant loss of callosal fibres in the splenium, anterior...
corpus callosum, genu, forceps major and forceps minor (see Fig. 3). We also found significant atrophy of the superior temporal gyrus in both hemispheres in the callosal group, as evidenced by a loss of grey matter on the left and increase of CSF on the right. There were no significant increases in white matter or grey matter in the damaged callosum group compared with the controls.

Performance data
There were no significant differences in accuracy between the three subject groups in the visual tasks \[F(2, 19) = 0.032, P = 0.96\] (Fig. 4A). For technical reasons, data were missing for one of the subjects in the preterm control group. For visual response times, the two-way ANOVA showed a significant main effect of group \([F(2, 539) = 12.6, P < 0.001]\), with the damaged callosum group significantly slower on both tasks. Although not reaching significance, Fig. 5A shows a pattern of response times in the damaged callosum group different from that of the control groups. Both preterm and term controls show a bilateral field advantage, with the bilateral comparison performed faster than the unilateral one. In contrast, the damaged callosum group shows a bilateral field disadvantage, with the response time to the bilateral stimulus being slower than that to the unilateral stimulus \([F(2, 529) = 1.2, \text{Hotelling’s trace} = 0.004, P = 0.3]\) (Fig. 5A).

The auditory task accuracy data showed a significant group effect. The damaged callosum group were least accurate, with mean and SDs for the damaged callosum group, preterm controls and normal controls, respectively, being 17.8 (3.9), 19.3 (3.8) and 20.6 (1.7) \([F(2, 19) = 3.85, P = 0.039]\) (Fig. 4B). Data were not available for one of the damaged callosum group.

As in the visual data, we found a significant group effect in the response time data, with the damaged callosum group significantly slower than the term and preterm controls \([F(2, 542) = 80, P < 0.001]\). There was a significant ear by group interaction, with the right ear response times slower than the left ear response times in the damaged callosum group, but no left ear–right ear differences in the control groups \([F(2, 542) = 3.02, \text{Hotelling’s trace} = 0.011, P = 0.05]\) (Fig. 5B).

There was also a significant effect of hand, independent of group or ear. The direction of the effect (right hand 100 ms faster than left) was in the opposite direction to the expected superiority of left hand over right for the right hemisphere timbre discrimination task. It was also much longer than previous estimates of callosal transfer time (i.e. Clarke and Zaidel, 1989). We therefore concluded that the hand effect identified was not due to callosal transfer but seemed instead to relate to hand dominance or task practice, as all subjects performed the left hand response experiments before the right hand response experiments. We therefore ignored the hand effect and pooled left hand and right hand experimental data in our fMRI analysis.

Differences in BOLD activation pattern between groups
Visual task (bilateral presentation > unilateral presentation)
Bilateral stimuli did not lead to significantly more activation than unilateral stimuli in either of the control groups. In contrast, the same comparison led to a significant difference in activity in the right dorsolateral prefrontal cortex (BA 9/10) of the damaged callosum group (Fig. 6). This difference between the groups was significant when we compared the damaged callosum group and term controls \((Z = 3.9; P = 0.04)\).
The same region was also significant in the damaged callosum–preterm control comparison using an a priori region of interest approach (search volume 0.5 cm sphere at x, y, z coordinates 38, 54, 24; Z = 2.8; P = 0.03) (Table 1). No regions were significantly more active in the control groups than the damaged callosum group, and there were no significant differences between the control groups.

**Auditory task (left ear presentation > right ear presentation)**

There were no significant activations for the left ear > right ear comparison in the term control group. In contrast, the preterm control group and the damaged callosum group showed activation of the right superior temporal gyrus (BA 22). The activation in the damaged callosum group was significantly greater than in either the term or preterm control groups (Z = 3.83; P = 0.05 full-term control; Z = 4.65; P = 0.04 preterm control) (Fig. 7).

Significantly more activity was also seen in the right precentral gyrus (Z = 4.32, P < 0.01) and left precentral gyrus (Z = 3.92; P = 0.04) of the damaged callosum group compared with the term control group. The same regions were active in the comparison of the preterm control group and the damaged callosum group using an a priori region of interest approach (search volume 0.5 cm sphere at x, y, z coordinates 44, −14, 58, Z = 4.24, P < 0.01 for right precentral gyrus; left precentral gyrus search volume 0.5 cm sphere at x, y, z coordinates −32, −12, 66, Z = 2.44, P = 0.04) (Table 2). No significant differences were seen between the full-term and preterm control groups, and no brain regions were significantly more active in the two controls groups than in the damaged callosum group.

**Discussion**

Our results show that preterm callosal damage affects behavioural performance and functional cerebral anatomy in early adulthood. The damaged callosum patients in our study could complete timbre and bilateral field comparison tasks, although at a reduced level of performance. One interpretation of the residual ability is that their callosal damage was insufficient to cause a performance deficit and that tasks were completed using the same neural mechanisms as found in normal subjects. However, the fact that we found significant differences in the task-related pattern of activity for the damaged callosum and control groups suggests that this was not the case. An alternative interpretation of the findings is that compromised callosal function has led to alternative neural strategies to compensate for the perinatal injury. In what follows, we examine the neural basis of this functional plasticity.

**Callosal-specific performance deficits**

In the visual task, the two control groups showed the normal pattern of behavioural responses, with reaction times for bilateral comparisons being faster than those for unilateral comparisons (i.e. Davis and Schmit, 1971; Dimond and Beaumont, 1971; Merola and Liederman, 1990; Norman et al., 1992). In contrast, the damaged callosum group showed the opposite pattern, with reaction times for unilateral comparisons being faster than those for bilateral ones. Our previous study of the cerebral activity underlying the bilateral field advantage suggested that bilateral and unilateral comparisons were carried out by different processing mechanisms, the bilateral comparison requiring a callosal transfer and the unilateral comparison requiring working memory resources. The results presented above support this hypothesis by revealing a bilateral disadvantage in subjects with a
damaged corpus callosum. Our fMRI results reveal how the damaged callosum group accomplishes the task. While normal subjects show no activity for the bilateral > unilateral comparison (Fig. 6) (Santhouse et al., 2002), the damaged corpus callosum group activates the dorsolateral prefrontal cortex in an area that previously has been associated with working memory (Braver et al., 1997; Cohen et al., 1997; Nystrom et al., 2000; Stern et al., 2000). One possible explanation for the delay in reaction time for the bilateral comparison in the damaged callosum group is that shapes

### Table 1

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The table shows x,y,z coordinates, cluster size and Brodmann area (BA) of the most significant voxel in each cluster. Also shown are the Z values and corrected P values. *Region examined with a priori hypothesis. For term and preterm control groups > callosum group and term > preterm control, preterm > term control, there were no differences in activation.

**Fig. 7** BOLD contrast in the comparison of the left versus right ear. One pair of ‘glass brain’ views (from the side and from above) is shown for each patient group for the left ear greater than right ear comparison (thresholding as for Fig. 6). The damaged callosum group shows a significant area of activation in the right superior temporal gyrus. This is significantly different from the term control group (left panel) and preterm control group (right panel), shown rendered onto an individual brain.
presented for comparison across a damaged corpus callosum are held ‘on line’ in working memory, to compensate for the impaired callosal transfer.

In normal individuals, the discrimination of timbre takes place largely in the right hemisphere (Sidtis, 1980; Samson and Zatorre, 1994; Platel et al., 1997). The specific areas identified in previous imaging studies include the superior and posterior temporal regions (Mazziotta et al., 1982) and the superior, middle frontal and precentral gyri (Platel et al., 1997). In theory, the right ear response time should be a few milliseconds slower than the left ear response times, as the right ear presentation requires a callosal transfer of signals for timbre discrimination (right ear→left hemisphere→right hemisphere). We did not find a significant difference in left and right ear reaction times in our two control groups as the number of trials presented in an fMRI experiment are insufficient to show such a small effect. In contrast, the damaged callosal group did show a significant difference in response times to left and right ear stimuli, with the right ear response, which in normal subjects requires a callosal transfer, being significantly slower than the left ear response. The pattern of brain activity elicited by the auditory stimuli provides an explanation for the behavioural effect. In control subjects, the right superior temporal gyrus would process timbre stimuli regardless of the ear of presentation, either by direct stimulation (left ear to right hemisphere) or through a callosal transfer (right ear→left hemisphere→corpus callosum→right hemisphere). The result is that there is no significant difference in activation of the region between left ear and right ear stimulation. In contrast, the damaged callosal group would be unable to perform an adequate callosal transfer from left hemisphere to the right, leading to an activation of the right superior temporal gyrus for left ear stimulation, but not for right ear stimulation (Fig. 7). We hypothesize that it is the inability to access the timbre discrimination area which underlies the slowing in reaction time for right ear stimulation. We also found additional left and right precentral gyrus activity in the damaged callosal group compared with the term controls. The right precentral gyrus has been associated with timbre processing in previous studies (Platel et al., 1997). An interesting question arises as to how the damaged callosal group are still able to perform the right ear task, even though their performance is impaired. One possibility is that they use the left hemisphere, and partial support for this comes from the fact that we found, using an a priori region of interest approach, significantly greater activation of the left superior temporal gyrus of the damaged corpus callosum group than the term control group for the right ear greater than left ear comparison (search volume 0.5 cm sphere at x, y, z coordinates 60, -32, 16; BA 22; Z = 3.0; P = 0.02).

**Non-specific performance deficits**

We found the damaged callosal group to be slower on both the visual and auditory tasks, regardless of whether they involved a callosal transfer. For the visual data, the longer response times enabled the callosal group to perform with accuracy equivalent to the two control groups. For the auditory data, the damaged callosal group were significantly less accurate [F(2,19) = 3.85, P = 0.039] despite the delay in response. The findings suggest that the callosal damage on MRI scans at age 14–15 years is associated with other more subtle brain abnormalities not apparent on the structural images. Another possibility is that the atrophy found in the anterior corpus callosum compromised the transfer of motor signals, introducing a delay in response time. We also found atrophy of the superior temporal gyrus bilaterally in the damaged callosal group. While this could have led to a non-specific deficit in the auditory task, it could not explain the non-specific deficit found in the visual task. It is unclear why this particular region is vulnerable; however, damage here raises an interesting possibility that it underlies language impairments found in preterm individuals during adolescence (Stewart et al., 1999)

**Methodological issues**

Our structural comparisons of grey matter, white matter and CSF images required normalization of each individual’s brain to a standard template. The procedure will therefore correct any overall differences in brain size between subject groups. However, the warping procedure does not attempt to match individual anatomical structures (the ventricles or specific

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gyri, for example), with the result that group differences at this anatomical level remain.

The overall performance deficit in the damaged callosum group confounds the interpretation of the fMRI data. An alternative interpretation of the activations is that they relate to task difficulty and not to differences in functional anatomy. To protect against this possibility, our analytical strategy was to compare differences between pairs of stimuli (e.g. bilateral versus unilateral) across groups rather than single stimuli.

The fMRI environment is uncomfortable, has distracting sounds and subjects are required to lie horizontally with their movements restricted. These stimulus conditions are different from those of the psychophysical laboratories in which reaction time experiments would normally take place. However, we do not think that the fMRI environment explains the non-specific deficits in the damaged callosum group, as the other two control groups were subject to the identical environment.

**Plasticity**

Functional compensation for brain injury is well described, with the greatest potential for plasticity seen in neonates (Bower, 1990). Early animal experiments demonstrated functional reorganization of the visual cortex after artificially induced visual impairment (i.e. Cynader and Mitchell, 1977; Cynader et al., 1981). Further studies showed that this functional reorganization is dependent on critical time periods during development (Hubel and Weisel, 1970; Pito and Lepore, 1983; Sherrard et al., 1986). Similarly, in humans, the time of injury is crucial to outcome—the earlier the lesion is sustained, the greater the potential for improvement (Lassonde and Sauerwein, 1997). Perinatal injury to the posterior corpus callosum, one of the commonest brain abnormalities found in individuals born very preterm (Stewart et al., 1999), occurs at a time where there is significant potential for functional reorganization of the visual and auditory fibres that pass through the posterior callosum. There is evidence that the compensatory mechanisms activated after damage may vary according to the sensory modality involved (Lassonde et al., 1990).

In our experiment, there appeared to be different categories of neural compensation following early callosal damage. In the auditory system, the fMRI evidence points to a left hemisphere or bilateral representation of timbre discrimination, rather than the right hemisphere specialization found in normals. In contrast, the activation of the dorsolateral prefrontal cortex in the visual experiment in the damaged callosal group implies the recruitment of working memory to compensate for impaired callosal function.

**Conclusion**

In summary, we have shown that both the structure and function of the adult brain are influenced by events occurring perinatally. The early damage sustained by the corpus callosum necessitates adoption of a different neural strategy for forced callosal transfer tasks. The exact nature of the change is dependent on the modality of the pathways affected.

**Acknowledgements**

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