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Disconnection of medial agranular and posterior parietal cortex produces multimodal neglect in rats

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Abstract

Two cortical areas in rats have been found to be important in directed attention and spatial processing: the medial agranular cortex (AGm), the rodent analog of the frontal eye fields; and the posterior parietal cortex (PPC), the rodent analog of area 7 in primates. As in primates, unilateral destruction of either of these cortical association areas produces severe contralesional neglect of visual, auditory, and tactile stimulation. AGm and PPC are reciprocally interconnected by longitudinally oriented axons traveling in layer VI of the cortex. Their trajectory provides a unique opportunity to examine the effects of disconnection of these two areas. The key question is whether these two regions function independently or as components of a cortical network for directed attention. Unilateral disconnection of the PPC and AGm was achieved via transverse knife-cuts extending through layer VI of cortex, and the disconnection verified by tract-tracing methods. The knife-cuts produced severe multimodal neglect and allesthesia/allokinesia. The deficits produced by the knife-cuts were virtually identical to those produced by unilateral destruction of these regions. The control operates, which received knife-cuts that spared the interconnections between the AGm and PPC, were unimpaired. The results indicate that AGm and PPC in rats function as parts of a cortical system for directed attention. © 1997 Elsevier Science B.V.

Keywords: Attention; Cortex; Disconnection; Neglect; Parietal; Prefrontal

1. Introduction

Neglect is a complex and devastating neuropsychological disorder affecting attentional, spatial, and cognitive processes [12]. In humans, neglect typically results from cortical damage to one of three multimodal convergence areas: the frontal eye fields, the inferior parietal lobule, or the cingulate cortex [11,12,26]. It has been suggested that these areas may form a corticocortical network mediating directed attention [12,19]. Anatomical and behavioral studies have suggested that the medial agranular cortex (AGm) and the posterior parietal cortex (PPC) are the rodent analogs of the frontal eye fields and the inferior parietal lobule in humans [3,14–17,20–23]. Unilateral destruction of either the AGm or the PPC produces severe neglect of visual, auditory, and tactile stimulation, and allesthetic/allokinetic responses that are qualitatively similar to those seen in humans with neglect [5,7,9,12].

The strong correspondence between the behavioral effects of unilateral AGm or PPC lesions raises the issue of whether these regions are functioning as relatively independent systems, or as an interconnected system for directed attention in space, as has been hypothesized for, but never directly tested in frontal and parietal areas in primates [12,19]. Anatomical investigations have indicated that areas AGm and PPC are highly interconnected [20,23], as are the frontal and parietal areas in primates [2,25], and support the contention that these regions are components of a cortical network for directed attention.

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Traditionally, primate models have been utilized to investigate the neural basis of neglect. However, utilizing the rodent model offers a distinct advantage. In primates, long-distance corticocortical axons travel in the white matter until arriving at their sites of termination [10,13,18,24]. In rats, however, many corticocortical axons including those interconnecting PPC and AGm travel longitudinally in layer VI of the gray matter [27]. Therefore, in rats these regions can be disconnected via a transverse knife-cut through the cortex which does not damage the white matter or areas AGm and PPC. In this study, we tested the hypothesis that AGm and PPC function as a cortical system mediating directed attention by severing their connections via transverse knife-cuts.

2. Materials and methods

2.1. Subjects

The subjects were ten male, adult, Long Evans hooded rats 120–180 days of age at the start of the experiment. As in prior studies from our laboratory, the subjects were handled daily for at least 2 weeks to gentle them for subsequent behavioral testing [5,14–16,31]. Following the 2 weeks of handling, the subjects were randomly assigned to either an experimental group ($n = 6$) or a control group ($n = 4$). Subjects were individually housed, and free food and water were available. Subjects were kept under a standard 12 h light/12 h dark cycle at all times.

2.2. Surgical procedures

Subjects were anesthetized with 0.35 cc/100 g Chloropent, ip. When totally unresponsive, as determined by the absence of a corneal reflex and absence of responsiveness to a mild tail pinch, the subjects were placed in a Kopf stereotaxic device. Blunt-tipped ear bars were used to prevent damage to the tympanic membrane. Using sterile instruments the scalp was incised and a portion of the skull removed at the desired coordinate location in the left hemisphere. A microsurgical blade holder (Fine Science Tools) fixed in the stereotaxic was used to make a mediolaterally oriented cut 1.5 mm in length and located just lateral to the cingulum bundle, near the rostral boundary of area PPC. For this purpose we utilized coordinates of 1.5–3.0 mm lateral to the midline, at an anteroposterior location 3.0 mm caudal to bregma. The depth of the cuts made in the experimental group was 1.7 mm, while those made in the control group were 0.9 mm. Gelfoam was placed in the area of exposure and surgical clips used to close the incision.

2.3. Behavioral testing

All behavioral testing was done with the experimenter blind with respect to the group membership of the subjects. The subjects were tested for neglect on the 3 consecutive days following surgery. Throughout the experiment, testing was conducted during the light phase of the light/dark cycle in a room with standard overhead fluorescent lighting. The orientation test was a modified version of that developed by Crowne and Pathria [7,8], and has been described in detail in previous studies [5,14,16].

Briefly, each subject was placed in its home cage on the testing platform for a 1 min period of adaptation. Then the animal was taken out of its cage, and placed directly on the test platform on which markings delineated 0, 30, 45, and 60° angles in either direction from a central line running the length of the testing board. The subject was gently restrained by hand from behind without restricting head movement, and was aligned with the center line on the board. Stimuli were presented only when there was no evidence of struggling, no asymmetry of body posture, and when the head was oriented in direct line with the body. Typically, the animal's body had to be realigned several times during testing. The early extensive handling minimized struggling and 'freezing' in the subjects. Visual, tactile, and auditory stimuli were then presented in turn. Previous studies have shown that order of presentation does not influence behavioral results [5,29]. The visual stimulus consisted of the presentation of a silver metallic rod 10.0 cm in length, which was waved in a small circle (approximately 5.0 cm in diameter) five times within the animal's visual field at a distance of 7.5–10.0 cm from the animal. The auditory stimulus was a single 114-dB (SPL) click generated by a clicking device held at midbody. The tactile stimulus was a single caudal-to-rostral stoke through the vibrissae with a 15 cm wooden Puritan applicator (Harkwood Products, No. 807).

Three cycles of testing comprised each test session. One cycle consisted of the single presentation of each of the three stimuli to each body side in turn. The experimenter rated the degree of head turning toward (appropriate responding) or away from (inappropriate, or allesthetic, responding) the stimuli as measured by the position of the tip of the snout over the test platform markings. A head turn of less than 30° was scored as zero, between 30 and 45° as 1.0, between 45 and 60° as 1.5, and greater than 60° as 2.0. Orientations made more than 2 s after stimulus presentation received a zero score. In addition, orientations to the visual stimulus after the third revolution (3 s) could only receive a maximum of 1.5. This modificaton of the scoring procedure was made to take into account the for long latencies (> 3 s) to respond to visual stimulation,

since presentation of the visual stimulus (approximately 5 s) lasted for a longer period of time than the tactile and auditory stimuli (approximately 1 s). Using this scoring method, the maximum score for appropriate responding on each body side is 6.0 for each of the three modalities, 18.0 in total. Previous studies have indicated that use of this rating scale produces an interrator reliability of 1.0 for the direction of orientation, and above 0.9 for the magnitude of orientation [5].

A total neglect ratio including the visual, tactile, and auditory orientation scores was derived from the formula (contralesional total responsiveness)/(ipsilesional total responsiveness). The neglect ratio is a measure of relative responding to each body side and takes into account total responsiveness as well as asymmetries in orientation behavior. Because the neglect ratio is dependent on the orientations in each of the modalities, individual modality neglect ratios were calculated using the formula (contralesional responsiveness − ipsilesional responsiveness)/(contralesional responsiveness + ipsilesional responsiveness). This ratio was utilized due to the large number of zero scores obtained in the individual modalities [28–32].

2.4. Anatomical methods

Following behavioral testing, animals were reanesthetized and placed in the stereotaxic apparatus. The brain surface was re-exposed and an injection of fluororuby (molecular probes) made 1.0–2.0 mm caudal to the cut. Pressure injections were made through glass micropipettes having tip diameters of 20–30 μm, using a Picospritzer (general valve) and 1–2 pulses of 2–40 psi, 3–10 ms duration, at each of three depths. After a postoperative survival time of 4 days, the animals were given 200 units of Heparin and a sodium pentobarbital overdose, then perfused intracardially with phosphate-buffered saline at 37°C followed by 4% phosphate-buffered paraformaldehyde containing 5% sucrose. The brains were extracted and post-fixed in cold 30% sucrose fixative for 1–3 days.

Sagittal frozen sections were cut at 30–40 μm on a sliding microtome, and collected into dilute fixative. Sections were stored in the refrigerator and mounted within a few days. Two spaced series of sections were mounted. One series was stained with cresyl violet and used for cytoarchitectural orientation. From these sections, drawings were traced using a macroprojector, and cortical boundaries indicated according to the criteria of Zilles and Wree [34]. Fluorescent labeled axons, neurons, and terminal fields were identified through the microscope, using a second series of unstained sections adjacent to the first. The locations of fluorescent labeled profiles were then plotted on the tracings, using features such as blood vessels for orientation. In the illustrations which follow, each line represents approximately 1–3 labeled axons, and each dot represents 1–3 labeled neurons [20,27]. The extent of damage produced by the knife-cuts was measured morphometrically using an IBAS-AT image analysis system. Histological analysis was done with the experimenter blind with respect to the group membership and behavioral performance of the subjects.

3. Results

3.1. Behavioral results

3.1.1. Total neglect ratios

As illustrated in Fig. 1, in contrast to the control group the experimental group demonstrated more severe neglect throughout the 3 days of testing. As found with lesion controls in prior studies [5,14,16,32] the control group demonstrated virtually symmetrical responding by Day 2 of testing. A group × days repeated measures analysis of variance (ANOVA) revealed only a significant effect of group ($F(1,8) = 54.58$, $P < 0.0009$). Follow-up t-tests with Bonferroni adjusted P-values ($P < 0.05$) were performed to compare the groups at each of the 3 days. The results indicated that the experimental group demonstrated significantly more severe total neglect than the control group on each of the 3 days of testing (Day 1, $t(8) = 4.06$, $P < 0.05$; Day 2, $t(8) = 4.68$, $P < 0.05$; Day 3, $t(8) = 6.75$, $P < 0.05$). The results indicate that the disconnection of PPC and AGm produced severe neglect in the experimental group.

3.1.2. Individual modalities

The results for the individual modalities are illustrated in Fig. 2.

3.1.2.1. Visual. The experimental group demonstrated more severe visual neglect than the control group

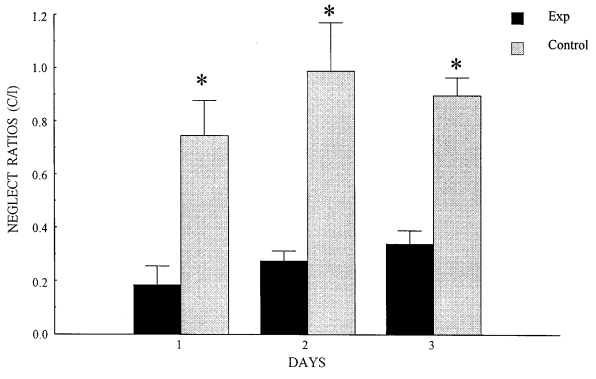

Fig. 1. Total neglect ratios for the experimental and control groups. A ratio of 1.0 represents symmetrical responding. All P-values < 0.05. * indicates a significant difference between groups. Error bars represent standard errors.

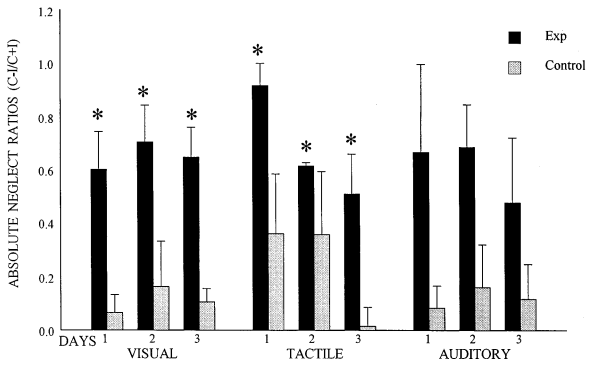

Fig. 2. Absolute modality neglect ratios for the experimental and control groups. A ratio of 0.0 represents symmetrical responding. Error bars represent standard errors and * indicates a significant difference between groups.

throughout the duration of testing. A group × days repeated measures ANOVA revealed a significant group effect ($F(1,8) = 27.01$, $P < 0.001$). Independent t-tests performed to compare the groups at each of the 3 days indicated that the experimental group demonstrated significantly more severe neglect on all 3 days (Day 1, $t(8) = 2.89$, $P < 0.02$; Day 2, $t(8) = 2.47$, $P < 0.04$; Day 3, $t(8) = 3.73$, $P < 0.007$).

3.1.2.2. Tactile. A group × days ANOVA revealed a significant effect of the group ($F(1,8) = 17.91$, $P < 0.004$), and the days ($F(2,16) = 9.26$, $P < 0.004$). t-tests for independent groups indicated that the experimental group demonstrated significantly more severe tactile neglect than the control group on each of the 3 test days (Day 1, $t(8) = 2.70$, $P < 0.003$; Day 2, $t(8) = 4.00$, $P < 0.006$; Day 3, $t(8) = 2.66$, $P < 0.04$).

3.1.2.3. Auditory. The group × days ANOVA indicated a significant main effect of the group ($F(1,8) = 6.53$, $P < 0.035$). Individual comparisons of the auditory neglect ratios for the experimental and control groups for each of the test days failed to reach significance.

3.1.3. Raw scores

In order to determine if group differences in neglect ratios were a result of changes in responsiveness on the contralesional body-side, the ipsilesional body-side, or both, separate analyses were performed using the raw score totals for each of the body-sides.

3.1.3.1. Contralesional. The group × days ANOVA revealed only a significant effect of group ($F(1,8) = 44.63$, $P < 0.001$). Follow up t-tests for independent groups with Bonferroni adjusted P-values were performed comparing the groups at each of the 3 days. The results indicated that the experimental group was significantly less responsive on the contralesional body-side than the control group on each day (Day 1: $t(8) = 4.25$, $P < 0.004$; Day 2: $t(8) = 5.13$, $P < 0.002$; Day 3: $t(8) = 3.42$, $P < 0.01$).

3.1.3.2. Ipsilesional. The group × days ANOVA comparing the ipsilesional raw scores revealed that the groups did not differ significantly in responsiveness to stimuli presented to the ipsilesional body-side.

The results of the analyses of the raw scores on the contralesional and ipsilesional body-sides indicate that the difference in neglect ratios between the groups was due to significantly less responsiveness (neglect) on the contralesional body-side in the experimental group.

3.2. Allesthetic/allokinetic responding

A group × days ANOVA indicated that the groups differed significantly in the amount of allesthetic/allokinetic responding on the contralesional body-side. The results revealed a significant group effect ($F(1,8) = 8.55$, $P < 0.02$). t-tests for independent groups with Bonferroni adjusted P-values performed for each of the 3 days indicated that the experimental group demonstrated significantly more allesthetic responses than the control group only on Day 3 ($t(8) = 3.68$, $P < 0.006$).

The group × days ANOVA comparing the amount of allesthetic/allokinetic responding on the ipsilesional body-side revealed no significant difference between groups.

3.3. Anatomical results

The mediolateral extent of the knife-cuts was comparable in the two groups, ranging from 1.0–1.4 mm. The rostrocaudal location of the knife-cuts in both groups ranged between area hindlimb (HL) and mid-PPC. As intended, the depth of the cuts in the experimental group affected layer VI in all cases, whereas the knife-cuts in the control group only reached layer V. The total extent of damage produced by the knife-cuts did not differ significantly between the two groups ($P > 0.05$), due to variability in the mediolateral extent of the cuts.

Case 253 (Subject 10) illustrates the basic axonal labeling pattern for the controls, which is virtually identical to that found in normal rats [27]. The knife cut extended into layer V (Fig. 3A, B) and appeared to cause minimal damage, as little gliosis was seen except in the immediate vicinity of the cut. The injection of fluororuby made caudal to the cut affected all layers of area PPC (Fig. 3A). Labeled axons are visible coursing rostrally and caudally from the cut. Most of these travel in the gray matter deep to layer V rather than in the white matter. Rostrally, they terminate in retrograde and anterograde labeling in area Fr2 (AGm) and the orbital cortex at the frontal pole (Fig. 3B, C). Caudally, they terminate in visual areas Oc2M and

Oc1. Other axons aggregate in the white matter and can be followed into the caudate-putamen and thalamus on more lateral sections.

Case 248 (Subject 5) illustrates the basic and axonal labeling pattern in the experimental cases. Here the knife-cut extended into the middle portion of layer VI (Fig. 4B, C). The injection of fluororuby in area PPC resulted in fewer labeled axons rostral to the cut, and only a few retrogradely labeled cells in the frontal pole, whereas there was extensive labeling caudal to the cut, in the visual cortex. In contrast, axons traveling in the subcortical white matter appeared to be unaffected by the knife cut, as they could be followed into the caudate-putamen and thalamus.

4. Discussion

The results of the present study indicate that disrupting the connections between areas AGm and PPC produces neglect which is strikingly similar to that produced by unilateral destruction of either the AGm or PPC [5,7,14,16,32]. Following either of these procedures, subjects demonstrate significant contralesional neglect for visual, tactile, and auditory stimulation, and allesthetic/allokinetic responding. The deficits produced by the knife-cut procedure are as severe as those found following unilateral destruction of the AGm, or PPC at an equivalent time post-surgery [5–7,14,16,32].

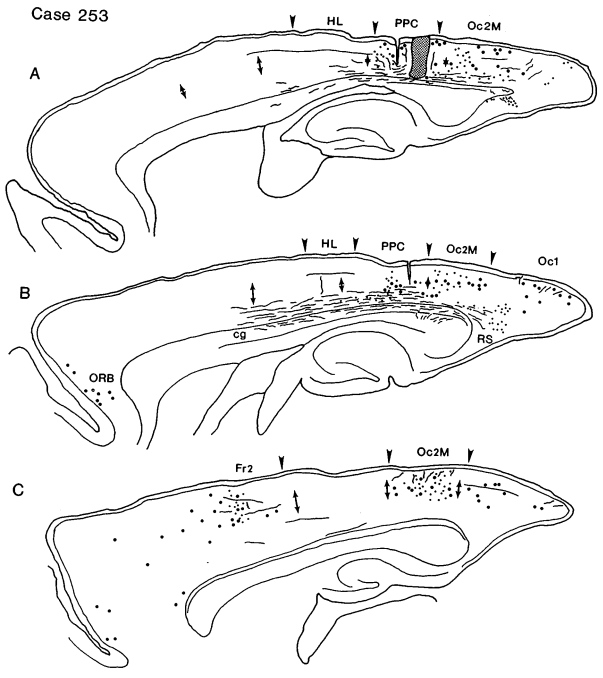

Fig. 3. Spaced sagittal sections from control Subject 10 (253), arranged in lateral to medial order, with the rostral pole to the left. Thin lines indicate the distribution of axons labeled by anterograde transport of fluororuby from the injection site (panel A) located just caudal to the knife-cut. Radially oriented arrows indicate extent of layer V. Abbreviations of cortical areas are done according to Zilles [34]; cg, cingulum bundle.

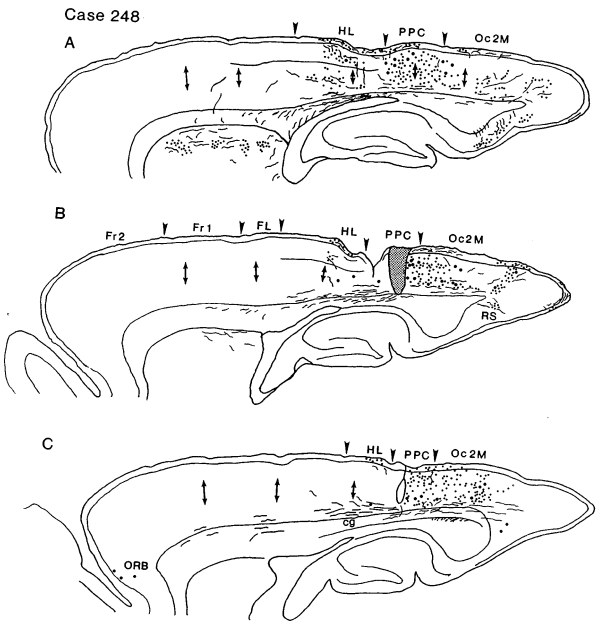

Fig. 4. Spaced sagittal sections from experimental Subject 5 (248); conventions as in Fig. 3. Note the greater depth of the knife-cut and reduced axonal labeling compared to the control case in Fig. 3.

The anatomical findings verified that the connections between areas AGm and PPC were severed by the deep transverse knife-cuts. Subjects in the experimental group exhibited fewer labeled axons traveling between PPC and AGm than subjects in the control group, however, some of the knife-cuts in both the control and experimental groups did produce minor damage to PPC. Nevertheless, severe neglect was demonstrated only in the experimental subjects, with or without damage to PPC (knife-cuts in HL). Therefore, the key factor was not extent of damage or areal location, but depth of the knife-cut and subsequent disruption of axons traveling in layer VI between AGm and PPC.

Another issue of some import may be the potential role of the close occurrence of behavioral testing to the surgical procedures. The results of this study were unlikely to be due to nonspecific surgical effects. In the present study the groups did not differ in lesion extent, but only the experimental group demonstrated severe neglect. Further, previous behavioral and pharmacological studies from our laboratories [6,14] have indicated that subjects can be tested within the immediate post surgical period [4–6,14] and will demonstrate a therapeutic response to apomorphine within 24–48 hr of surgery [4,5].

The present results lend support to the contention that areas AGm and PPC are functioning together as part of the circuitry which mediates directed spatial attention in rodents. These results also hold some impli-

cations for the interpretation of lesion studies of the AGm. King and Corwin [16] found that severe neglect was produced by relatively selective destruction of the caudal component of AGm whereas lesions of more rostral AGm did not produce severe neglect. The results were interpreted as indicating that destruction of the caudal AGm was essential to produce severe neglect. In light of the present findings, caudal AGm lesions may have destroyed some of the axons traveling through layer VI between AGm and PPC thereby resulting in neglect via a disconnection of AGm and PPC. This issue needs to be addressed directly by using neurochemical techniques that selectively damage cell bodies while sparing axons of passage.

Pharmacological studies utilizing the rodent model of neglect have implicated striatal dopaminergic and glutamatergic mechanisms in neglect and behavioral recovery from neglect induced by unilateral destruction of AGm [5,16,28,30–32]. Recent studies have focused on projections from AGm to the dorsolateral quadrant of the caudate [22,28,30,31]. However, in the present study these connections were not interrupted by the knife-cuts. Taken together, these results suggest the importance of a cortical-subcortical circuit for directed spatial attention which includes AGm, PPC, and the dorsolateral quadrant of the caudate. The relationships between these areas could be further tested by examining the pharmacological effects of knife-cuts. Furthermore, because dopamine agonists partially reinstate normal functioning following unilateral lesions of AGm, it would be instructive to determine whether dopamine agonists would also result in recovery of function from neglect following knife-cuts.

Though the results of the present study suggest that the AGm and PPC function as components of a system for directed attention, the specific nature of the failure of orientation remains to be determined. Neglect in our testing situation may result from a failure of stimulus detection, a motor output problem [1,33], or an interaction between the two. This is also the case when trying to distinguish allesthesia from allokinesia. Many of our studies have used the term allesthesia for inappropriate orientations. However, the finding of significant allesthesia/allokinesia suggests that for at least some sensory presentations that the sensory signal may be reaching the system but that the motor response is degraded in some way. The role of dopaminergic mechanisms in neglect and behavioral recovery from neglect in rodents [4,5,16,28,32] and humans [9] following cortical lesions which induce neglect certainly lends support to the contention that there is a motor output problem. To make this determination will require futher behavioral studies with alternative testing methods which allow for distinguishing sensory and motor contributions to cortically induced neglect [1].

The results of the present study demonstrate that areas AGm and PPC can be disconnected via a transverse cortical knife-cut without causing extensive damage to the subcortical white-matter. This is possible in rats because the connections of AGm and PPC travel in layer VI of the cortex, rather than in the subcortical white-matter [27]. These anatomical and behavioral findings demonstrate that the rodent model provides a unique opportunity to examine the neural basis of neglect, and to investigate the interactions between the parietal and prefrontal association cortices.

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