Cortical Functional Anatomy of Voluntary Saccades in Parkinson Disease

'Jochem W. Rieger[1], Aleander Kim[2], Miklos Argyelan[2], Mark Farber[3], Sofya Glazman[2], Marc Liebeskind[4], Ivan Bodis-Wollner[2]

[1]Dept. of Neurology II Otto-von-Guericke-University, Magdeburg, Germany, [2]Dept. of Neurology, SUNY Downstate, Brooklyn NY, [3]Graduate School of SUNY Downstate, Brooklyn NY, [4]Park Avenue Radiology Associates, New York, NY

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Corresponding author:
Ivan Bodis-Wollner M.D., D.Sc.
Dept. of Neurology
State University of New York
Downstate Medical Center
Brooklyn, New York 11203
USA
Phone: +1 718 270 1482
Fax: +1 718 270 3840
Email: Ivan.Bodis-Wollner@downstate.edu

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ABSTRACT

In Parkinson Disease (PD) several aspects of saccades are affected. The saccade generating brainstem neurons are spared, however the signals they receive may be flawed. In particular voluntary saccades suffer, but the functional anatomy of the impairment of saccade related cortical control is unknown.

We measured blood-oxygenation-level-dependent (BOLD) activation with functional Magnetic Resonance Imaging (fMRI) while healthy participants and patients with PD performed horizontal voluntary saccades between peripheral visual targets or fixated centrally. We compared saccade related BOLD-activity vs. fixation in patients with PD and in healthy controls and correlated perisaccadic BOLD-activity in PD patients with saccade kinetics (multistep saccades). Saccade related BOLD-activation was found in both, PD and healthy participants in the superior parietal cortex (PEF) and the occipital cortex. Our results suggest remarkable hypoactivity of the frontal and supplementary eye fields (FEF and SEF) in PD patients. On the other hand, PD patients showed a statistically more reliable BOLD modulation than healthy participants in the posterior cingulate gyrus, the parahippocampal gyrus, inferior parietal lobule, precuneus and in the middle temporal gyrus.

Given abnormal frontal and normal PEF responses, our results suggest that in PD a frontal cortical circuitry, known to be associated with saccade planning, selection, and predicting a metric error of the saccade, is deficient.

INTRODUCTION

We constantly make saccades as we explore our environment and shift our attention to visual details of interest. The movement characteristics of saccades, such as amplitude, duration and onset time can be described by standardized methods. Additionally, functional imaging greatly contributes to our knowledge about the functional organization of saccades. Here, we

studied the cortical organization of voluntary saccades which are closely linked to cognitive functions that enable us to explore the world.

In Parkinson Disease (PD) the saccade generating brainstem neurons and the eye muscles are spared, nevertheless saccades are impaired[1-7]. In PD, in contrast to relatively spared performance on reflex saccade tasks, voluntary[8] and non-visually guided saccades suffer[9]. Instrumental studies reveal several abnormalities such as hypometry, slowing of the saccade velocity, and delayed saccade onsets[8]. Clinically, it can be observed in some patients that saccades are fragmented into several steps, rather than being strictly ballistic. However, the anatomy of voluntary saccade related cortical activity is hitherto unknown in PD.

We therefore studied the cortical topography of perisaccadic activation (i.e. the activation around the saccade event) in patients with PD and in healthy participants using functional magnetic resonance imaging (fMRI). Our study shows the first time, that using a simple paradigm for voluntary saccades, the frontal brain areas involved in eye movement planning and execution and monitoring are selectively affected in PD.

METHODS

Participants

Nine patients with PD (mean age 77.7 years ± 12.8 years standard deviation) and six healthy controls (53.7 years ± 14.0 years standard deviation) volunteered in the study. Written informed consent was obtained from all participants prior to their participation in the study. The experimental protocol was approved by the SUNY Downstate medical Center's Institutional Review Board.

All PD patients were evaluated with the Unified Parkinson Disease Rating Scale (UPDRS) and mini mental status examination (MMSE) scores were obtained. Their average UPDRS motor score at the time of the investigation was 32 (± 10.8 standard deviation). None of the PD patients exhibited signs of clinical depression and major psychosis. All PD patients were

non-demented by criteria of the MMSE. Each individual scored above 28 (mean 29.6, range 28 to 30). Dropped points were not related to the visuospatial component of the MMS. None of the patients included in this study were hallucinators.

Seven out of the nine patients were additionally tested with a battery of neuropsychological tests included in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). This is a brief test measuring attention, language, visuospatial/constructional abilities, and immediate and delayed memory. It contains a number of subtests including line orientation. The following areas of neuropsychological functioning were of potential relevance to our findings of hypoactive frontal eye fields:

Three visual spatial tests were administered: 1) The RBANS Line Orientation subtest (similar to the Judgment of Line Orientation Test). 2) The RBANS Figure Copy subtest is similar to the Rey-Osterrieth Complex Figure Test. The individual must copy a relatively complex geometric design and then draw it from memory 30 minutes after presentation. 3) The Benton Visual Form Discrimination Test (VFDT) is a 16-item multiple choice (no motor requirements) test that measures complex visual recognition. Each of the 16 VFDT items consists of a target set of stimuli and four sets of response stimuli in which one set is a precise match and the other three contain distortion, displacement, or rotational errors. Attention was assessed by two RBANS subtests: 1) The RBANS Digit Span subtest is similar to the WAIS-III Digit Span forward test. It measures auditory short-term memory, sequencing skills, attention, and concentration. The task involves rote learning and memory, attention, encoding, and auditory processing. 2) The RBANS Coding subtest is similar to the WAIS-III Coding subtest. It assesses processing speed and involves short-term memory, learning ability, visual perception, visual-motor coordination, visual scanning ability, cognitive flexibility, attention, motivation and visual and sequential processing. Attention was impaired in 2, low average in 2, and high average in 2 patients. In one patient the test was incomplete. Visuospatial

orientation was borderline in 1 patient, low average in 1, high average in 4, and incomplete in 1. None of the patients exhibited neglect as tested with double simultaneous stimulation.

It has been reported that Levodopa medication slows prosaccades and improves antisaccades (Hood et al., 2007). In our study 4 patients were on Levodopa, three of whom in addition received amantadine and one received selegilin in addition. Five patients were not treated with dopaminergic medications but one of them received amantadine. Treated patients were tested between 1 hour and 2 hours following their morning medication.

Paradigm

BOLD activation related to saccadic eye movements in both PD patients and healthy controls was studied in a paradigm with alternating blocks of central fixation and voluntary saccades between two peripheral targets. Each block lasted 35 s. During saccade blocks participants performed saccades at a self paced rate between the peripheral targets, each 17 deg/visual angle to the left or right from the screen center. During fixation blocks only the central fixation cross was visible and during saccade blocks only the peripheral targets were presented. Fixation and saccade targets were white crosses on a gray background projected (Epson Powerlite 54c LCD projector) onto a screen located at the scanner bore and viewed via a mirror attached to the head coil. Prior to fMRI-scanning each participant performed a practice run presented on a Laptop screen outside the scanner to accommodate to the task and to make sure the task was fully understood.

During fMRI-scanning eye-movements were monitored with a video camera. More quantitative measurements were done outside the scanner.

Eye movement analysis and multistep saccades

Eye movement analysis was performed for five of the PD patients using a RK-726I Iscan eye-tracking system. The participants placed their head on a chin-rest stationed one meter from a computer screen (IDEK Vision Master). Instructions given for eye movements outside the

scanner were the same as for fMRI scanning. PD patients were asked to move their eyes between two dots placed 17 deg/visual angle away from the screen's center. Target directed saccades of PD patients are often broken down into a rapid sequence of multiple smaller saccades instead of one large saccade. We counted for each subject the number of multistep saccades. The relative proportion of multistep saccades in the total number of saccades in each of these PD-patients was then used for a group correlation analysis against the fMRI data.

Image acquisition

MR-scanning was performed with a 1.5T Siemens Magnetom Symphony scanner. For functional BOLD-imaging thirty-six axial slices covering the whole head were obtained with a gradient-recalled-echo sequence (repetition time 3.5 s, echo time 50 ms, field-of-view 24 cm, voxel size: 3.75x3.75x3.00 mm, image matrix 64x64 voxels). Ten functional volumes were acquired per experimental block. At least one-hundred volumes were obtained in total per subject. Additional high-resolution T1-weighted structural MRIs were acquired using a 3D-MPRAGE sequence in the same scan session.

Image analysis

Functional data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). First, images of each time series were spatially realigned to the first image of the time series and realignment parameters where checked to confirm that none of the subjects had moved more than 4 mm. The functional and anatomical scans were then spatially normalized to the Montreal Neurological Institute (MNI) space average brain. The normalized functional images were then spatially smoothed with an 8 mm FWHM Gaussian kernel on all subjects. The statistical analysis was performed using a standard General Linear Model approach. The regressors were calculated by convolving the block design function with a standard hemodynamic response function. In addition, the head movement parameters obtained during spatial realignment were modeled as effects of no interest. The resulting

individual contrast volumes were used in a second level analysis to compare within groups between conditions. The MNI-coordinates were transformed to Talairach coordinates using mni2tal (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

RESULTS

In order to examine the impact of Parkinson disease on the saccadic system we compared BOLD-activation during voluntary saccades between PD patients and healthy control participants. Moreover, we investigated the correlation between multistep saccades vs. voxel activations in PD patients. Due to the limited temporal resolution of the BOLD-response we cannot discriminate pre-, intra- or post-saccadic activation modulations. For that reason we denote the activation reported here “perisaccadic” to indicate that this activation is elicited around the time of a saccade.

Voluntary saccades: control participants

Figure 1A shows the activation clusters in the contrast voluntary saccades > fixation for healthy participants thresholded at $p<0.001$ with 10 voxels minimum cluster size. The glass brain images in Figure 1 show the projection of the strongest effects in saggital, axial and coronal direction. They provide an excellent overview over the spatial distribution of significant BOLD-modulations simultaneously over the whole brain. Increased BOLD-activations during voluntary saccades were predominantly found in the medial frontal area in the region of the supplementary motor area, which we consider as supplementary eye fields (SEFs), bilaterally to SEF in the frontal eye fields (FEFs), and in the parietal eye fields (PEFs) in the superior parietal lobe. These regions are part of a cortical network involved the control of saccades[10, 11, 12]. Moreover, a relatively small activation cluster was found in the visual cortex, in the cuneus in Brodmann area (BA) 18. Table 1 lists the Talairach-coordinates of the clusters exceeding corrected cluster significance level at $p<0.05$[13].

Figure 1 about here

Table 1 about here

Voluntary saccades: PD patients

Figure 1B shows the activation clusters in the contrast voluntary saccades > fixation for PD patients thresholded at p<0.001 with 10 voxels minimum cluster size. Table 2 lists the Talairach-coordinates of the clusters exceeding corrected cluster significance level at p<0.05. The most important difference to the results obtained with healthy participants was a shift of the BOLD-effects to more posterior brain areas. The most reliable effects were found in the in two large bilateral posterior clusters. These clusters contain local maxima in the lingual gyrus (BA 18 and BA 19), extend anterior into the parahippocampal gyrus (BA 30), into the posterior cingulate (retrosplenial) cortex (BA 30). Another activation cluster was found lateral in the inferior temporal gyrus (BA 37) in the right hemisphere.

In PD patients a BOLD-activation cluster in the superior parietal lobe was found in a location close to an eye-movement related BOLD-activation cluster in healthy participants (Talairach coordinates in PD patients: -16.0, -65.0, 51.0, in healthy participants: -24, -65, 53). However, in the analysis of the PD patient data this cluster exceeded only the liberal criterion (p<0.001 uncorrected, 10 voxels min. cluster size) but not the more conservative criterion (p<0.05 corrected at cluster level). We consider this as a weak effect. Although all nine patients performed the required saccade task (both outside and inside the scanner), the frontal eye movement related effects observed in healthy participants are missing in PD patients. This suggests that not only the parietal effect but also the frontal eye-movement effects are much weaker in PD patients than in healthy participants.

Table 2 about here

Correlation analysis: multistep saccades vs. voxel activations

Here we analyzed the relationship between multistep saccades in PD patients and BOLD-activation in PD patients. For each of the 5 PD patients we correlated the percentage of

multistep saccades with the BOLD-modulation derived from fMRI data. The glass brain images in Figure 1C shows clusters with correlations significant at an uncorrected level of $p<0.001$ and at least 10 voxels in size. The largest cluster was found in the medial frontal gyrus (Brodmann area 6) of the SEF. This cluster was statistically significant at the corrected cluster level with $p<0.001$. A smaller significant cluster was found in the precentral gyrus. Table 3 lists the Talairach-coordinates of the clusters exceeding corrected cluster significance level at $p<0.05$.

Table 3 about here

DISCUSSION

Abnormalities of reflex saccades to novel visual stimuli in patients with moderate and severe PD are slight[8], but voluntary saccades show several impairments, such as hypometric and multistep saccades. For instance, self initiated saccades, made in anticipation of the appearance of a target or to a remembered target location, show increased mean latencies, decreased degree of accuracy and higher error rates in PD[14].

Our study shows that the cortical frontal eye fields are profoundly affected when patients with PD execute *voluntary* saccades. As expected, in healthy participants saccade related cortical BOLD-activation was predominantly found in the frontal eye fields (FEF), the supplementary eye field (SEF), the superior parietal cortex (PEF) and in occipital cortex[10-12, 15-18]. In fact, in this simple voluntary saccade paradigm a deficit in the frontal eye fields is not the only abnormality we found: the overall distribution of the activation clusters is remarkably different in healthy and PD patients. PD patients seemed to show more overall above threshold voxels (about 40% more) than healthy controls did. This result makes it even more remarkable that PD patients had no above threshold frontal activity.

Our findings are in contrast to the effect of aging on BOLD-fMRI during prosaccades and antisaccades[12]. Raemaekers et al.[12] have shown that there is an age related shift in relative activity between posterior and frontal brain regions as a result of aging. Young healthy adults showed stronger posterior than anterior activation while in older adults this difference diminished suggesting a relative shift of activation. Clearly, our fMRI-results cannot be attributed to aging at all. In fact, the results reported by Raemaekers et al. would predict no difference between anterior vs. posterior activation in our aged PD patients. However, the reduced perisaccadic cortical activity for voluntary saccades in PD is compatible to the reported frontal metabolic hypoactivity in PD[19]. Rather than aging, the shift of activity between anterior and posterior cortical areas in PD raises the possibility of a reorganization of saccade related cortical areas for voluntary saccades. It has been shown that cortical reorganization occurs in PD, for instance for voluntary finger movements[20].

Moreover, it is unlikely that the differences in the frontal BOLD-activation patterns in the PD-group and the control group are due to the different number of subjects in the groups. Different group sizes could make numerically similar differences in the larger group exceed statistical significance threshold while significance is not reached in the smaller group. However, in this case one would expect significant frontal BOLD-activations in the larger PD-group but not in the smaller control group. In our study we found the opposite effect.

In the following we discuss several possible explanations of our fMRI-results in relation to monkey studies and imaging results in healthy human subjects.

Perisaccadic SEF and FEF activity: selection, prediction and error monitoring

Activity in the SEF[10-12, 21, 22] is predominantly elicited in saccade paradigms which require either suppression of pro-saccades, or implementing task instruction for saccade direction, or a switching between strategies[23]. In the PD group analysis comparing mean activation levels there was no SEF activity above threshold level. However, it is worth mentioning that we

further analyzed individual BOLD data in PD and correlated individual BOLD-activity with the number of steps patients made when performing a saccade. One of the pathological hallmarks of saccades in PD is “spontaneous” multistepping. To our surprise only SEF activity had a positive correlation with multistepping, that is the more saccadic steps, the higher the activity in SEF. It is known that SEF is involved in the initiation of voluntary (not reflex) movement and in “conflict” monitoring[24, 25]. Based on this physiological evidence, one could consider that SEF neurons contribute to both eye movement selection control and error correction of voluntary saccades. In that vein of thought multistep saccades may represent an effort for compensation. However, further studies are needed to evaluate this interpretation of the role of SEF in adaptability of saccades in PD.

Moreover, the medial frontal region around SEF is known to be affected in progressive supranuclear palsy [26]. In this PD related neurodegenerative disease vertical eye movements are severely and initially affected, unlike in early idiopathic PD. Low amplitude or slowed up gaze in PD is well known, although minor compared to the evident abnormality in progressive supranuclear palsy[5]. Clearly, further studies may be helpful de distinguish cortical functional anatomy of vertical and horizontal saccades in PD.

Perisaccadic FEF activity can start as a result of the planned saccade in advance of a target which will appear in the receptive field of the neuron[27]. Human transcranial magnetic stimulation studies in double step saccade paradigms suggest that the FEF maintains retinotopic coordinates for upcoming saccades or in predicting metric errors for the saccade[28]. The lack of perisaccadic FEF activation is of particular interest as the FEF is reciprocally connected with the basal ganglia via thalamocortical circuits[29]. Based on this closed loop one may assume that FEF hypoactivity in PD is not restricted to FEF, i.e. the relevant basal ganglia function is also affected. Given the known basal ganglia pathology of PD, this suggestion is not unreasonable.

Visuo-spatial impairment and voluntary saccades in PD

Space exploration comprises tasks such as the ability to scan the environment and to move the body to interact with this environment. PD patients have problems with both. It is thought that PEF is primarily involved in spatial motor and attentional aspects of saccades. Spatial attention and saccades sometimes called “covert” and “overt” attention engage overlapping cortical areas. In our study healthy controls showed PEF effects while PD patients, showed perisaccadic PEF activation only at a more liberal threshold level. FEF and SEF activities were, however, still not reaching this lower threshold. Some fMRI studies in normal subjects revealed a co-involvement of eye movement related areas in overt and covert attention shifts[30, 31], others did not[32, 33]. However, this might be due to paradigm differences. In our study we did not manipulate covert attention. Further studies are required to evaluate the neuropsychological significance of perisaccadic PEF activity in PD.

Increased BOLD-effects in PD brains: anatomical considerations

We found that FEF is deeply and PEF is somewhat hypoactive in PD while posterior, activity in the occipital, the medial inferior posterior parietal, and the posterior temporal lobe is far stronger in PD than in healthy controls. It is possible that decreased frontal and parietal activity is instrumental in increasing the spatial extent of occipital activation. The FEF projects to the mediodorsal nucleus and then to the cortex[29]. Moreover, the PEF connects to the superior colliculus (SC) which in turn projects to the ventral pulvinar, which is reciprocally connected to almost all visual cortices[34] and has an inhibitory influence on occipital cortices. If so, weakened PEF activity may also increase occipital activation.

BOLD activity in the precuneus, is associated with spatial memory[35] even during saccades and blinks[22]. The posterior cingulate and parahippocampal gyrus which are associated with deficits in topographical amnesia and agnosia were spared or even showed increased perisaccadic activity in PD patients[36, 37]. This would imply that our saccade paradigm placed

some demand on these areas which were not affected by PD pathology in these patients whose MMS was normal.

CONCLUSION

Based on the information from monkey studies and human fMRI results of saccades, our fMRI results suggest that in PD a frontal neuronal circuitry, underlying saccade direction selection is deficient while activation in several posterior brain areas associated with saccades is increased. These reciprocal effects indicate a shift of brain activation between frontal and posterior activation in PD for voluntary saccades.

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Tables

Table 1

Voluntary Saccades: healthy participants' activation clusters

Brain area	BA	Talairach coordinates			Voxels	Z value
		X	Y	Z		
Superior Frontal Gyrus (L)	6	-6	12	55	195	4.65
Precentral Gyrus (L)	6	-55	-2	35	37	4.76
Precentral Gyrus (L)	6	-28	-7	52	139	4.29
Superior Temporal Sulcus (L)	42	-67	-32	20	49	4.33
Inferior Parietal Lobe (L)	40	-36	-42	50	24	3.82
Superior Parietal Lobule (L)	7	-24	-65	53	95	4.12
Cuneus (L)	18	-12	-79	15	21	3.85
Middle Frontal Gyrus (R)	6	28	0	42	49	4.08
Superior Parietal Lobe (R)	7	30	-53	60	35	3.66
Cerebellum (R)		30	-65	-20	78	3.72

All reported clusters pass a corrected cluster significance level at $p<0.05$. Talairach coordinates are reported for the cortical voxel exhibiting the maximum effect in the cluster. The Brodmann areas (BA) covered by the activation clusters are listed in the second column.

Table 2

Voluntary saccades: PD patients' activation clusters

Brain area	BA	Talairach coordinates			Voxels	Z value
		X	Y	Z		
Lingual gyrus (L), parahippocampal gyrus (L), posterior cingulate (retrosplenial) cortex (L), precuneus (L)	18, 19, 30, 31	-8	-60	5	496	4.08
Inferior temporal gyrus (R)	37	55	-54	-1	53	4.39
Lingual gyrus (R), parahippocampal gyrus (R), posterior cingulate (retrosplenial) cortex (R)	18, 19, 30	8	-77	6	339	3.98

All reported clusters pass a corrected cluster significance level at $p<0.05$. Talairach coordinates are reported for the cortical voxel exhibiting the maximum effect in the cluster.

Table 3

Correlation analysis: PD patients' correlation clusters

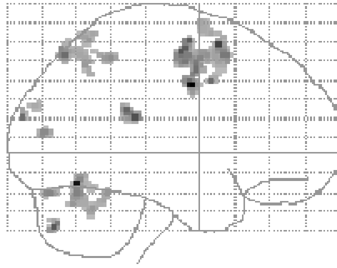
Brain area	BA	Talairach coordinates			Voxels	Z
		X	Y	Z		
Medial Frontal Gyrus (R)	6	12	3	51	55	4.16
Precentral Gyrus (R)	6	22	-9	48	11	4.22

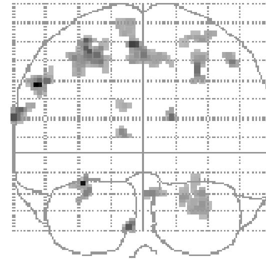
All reported clusters pass a corrected cluster significance level at $p<0.05$. Talairach coordinates are reported for the cortical voxel exhibiting the maximum effect in the cluster.

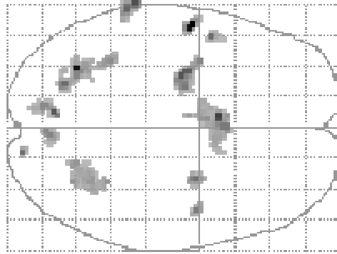
Figure legend

Figure 1. A) Glass brain images depicting voxels exceeding an uncorrected threshold of $p<0.001$ in the group comparison voluntary saccades vs. fixation for healthy participants. The minimum cluster size is 10 voxels. Note that the effects we consider as statistically significant pass a more conservative criterion of $p<0.05$ corrected for multiple comparisons at cluster level. B) The group results for the comparison voluntary saccades vs. fixation for PD patients. Thresholds are analogous to A). C) The results of a correlation between BOLD activation and percentage of multi-step saccades in PD patients. The threshold was chosen as in A).

A

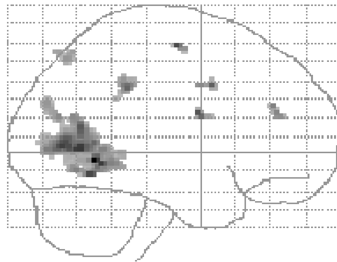


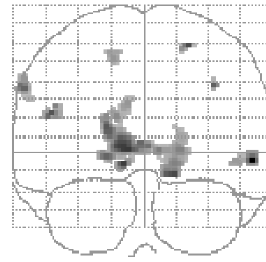


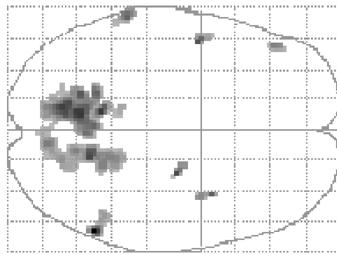


Healthy participants:
voluntary saccades
>
fixation

B

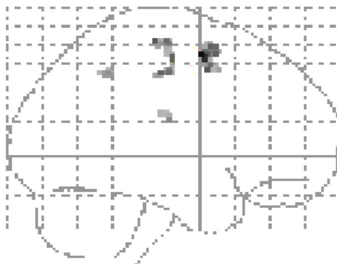


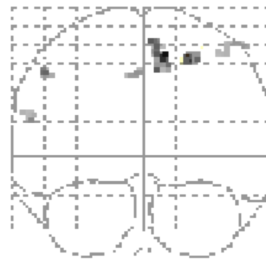


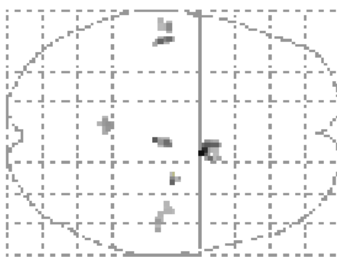


PD patients:
voluntary saccades
>
fixation

C







PD patients:
multistep saccade
correlation