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Visuospatial processing in children with neurofibromatosis type

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Abstract

Neuroimaging studies investigating the neural network of visuospatial processing have revealed a right hemisphere network of activation including inferior parietal lobe, dorsolateral prefrontal cortex, and extrastriate regions. Impaired visuospatial processing, indicated by the Judgment of Line Orientation (JLO), is commonly seen in individuals with Neurofibromatosis type 1 (NF-1). Nevertheless, few studies have examined the neural activity associated with visuospatial processing in NF-1, in particular, during a JLO task. This study used functional neuroimaging to explore differences in volume of activation in predefined regions of interest between 13 individuals with NF-1 and 13 controls while performing an analogue JLO task. We hypothesized that participants with NF-1 would show anomalous right hemisphere activation and therefore would recruit regions within the left hemisphere to complete the task. Multivariate analyses of variance were used to test for differences between groups in frontal, temporal, parietal, and occipital regions. Results indicate that, as predicted, controls utilized various right hemisphere regions to complete the task, while the NF-1 group tended to recruit left hemisphere regions. These results suggest that the NF-1 group has an inefficient right hemisphere network. An additional unexpected finding was that the NF-1 group showed decreased volume of activation in primary visual cortex (BA 17). Future studies are needed to examine whether the decrease in primary visual cortex is related to a deficit in basic visual processing; findings could ultimately lead to a greater understanding of the nature of deficits in NF-1 and have implications for remediation.

Keywords

Neurofibromatosis; visuospatial processing; JLO; Judgment of Line Orientation; fMRI

Neurofibromatosis Type-1 (NF-1) is a common genetic disorder affecting the nervous system with a prevalence rate of approximately 1:3000 to 1:4000 (NINDS, 2007). Individuals with NF-1, in addition to having physical characteristics including café-au-lait spots, multiple neurofibromas, and bone deformities, also have a high incidence of macrocephaly, optic

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gliomas, T2-weighted hyperintensities (UBOs), and learning deficits (Cutting, Koth, & Denckla, 2000; Cutting et al., 2004; Feldman et al., 2003; Goh et al., 2004; Hofman et al., 1994; Hyman et al., 2003; North et al., 1994; North et al., 1995). Studies have shown that individuals with NF-1 have cognitive deficits in both language and visuospatial domains; however, visuospatial impairment has long been considered a hallmark feature of the disorder, especially on the Judgment of Line Orientation test (JLO; Moore & Denckla, 1999). For example, Schrimsher et al. (2003) demonstrated that visuospatial performance represents a strong predictor of NF-1 diagnosis, finding that children with NF-1 had a particular pattern of performance on visuospatial measures that could correctly identify 90% of over 100 children and adolescents with NF-1. Additionally, there may be linkages between the visuospatial impairment and verbally-related impairments in NF-1. For example, Levine et al. (2006) examined the relationship between reading and visuospatial measures in children with NF-1. Although both the NF-1 and RD groups showed poor phonological processing (consistent with poorer reading abilities), for children with NF-1, all single word-reading measures correlated significantly with almost all of the visuospatial ability measures, whereas for the Controls and RD groups they did not. Results from this study suggest that visuospatial skills may be related to reading performance in some manner in NF-1 and therefore it may be important to understand the origin and nature of this relationship to understand the cognitive profile of NF-1.

Although, behaviorally, visuospatial deficits have been identified in individuals with NF-1, to date, only one study has examined the neural activity associated with visuospatial processing as revealed by functional neuroimaging (Billingsley et al., 2004). In this study, Billingsley et al. (2004) used an alphanumeric task with two different spatial transformation conditions: mirroring and rotation. It was found that individuals with NF-1 utilized posterior cortex, including occipital, parietal, and middle temporal cortices, to a greater degree than controls relative to lateral and inferior frontal regions. From the results, it was suggested that anomalies in frontal cortex existed in individuals with NF-1 and that this could be used as evidence for a neural substrate marker for cognitive deficits. Nonetheless, a sub-sample of the NF-1 participants met criteria for having problems with reading and the functional task used consisted of alphanumeric stimuli. Therefore, the under utilization of inferior frontal cortical regions could in part be related to reading disability present in the NF-1 sample, as utilization of the inferior frontal cortex is implicated in reading-related tasks.

The objective of the present study was to investigate the neural activity associated with visuospatial processing, in particular on the JLO, for individuals with NF-1. Previous studies using this type of task have revealed patterns of activation in a right hemisphere network including inferior parietal lobe, dorsolateral prefrontal cortex, and extrastriate regions (Ng et al., 2001; Kesler et al., 2004). Accurate JLO performance has been tied to basic visual processing, including secondary and tertiary visual cortices, by Ng et al. (2001). Additionally, individuals with Turner Syndrome, a genetic disorder also exhibiting visuospatial impairments, have shown relative underactivation of parietal and occipital cortices while completing a JLO task (Kesler et al., 2004). We hypothesized that we would see differences in patterns of activation, denoted by volume of activation measured within predefined regions of interest, indicating an inefficient visuospatial processing system that could be represented in several ways. We hypothesized that the NF-1 group would show an increased volume of activation in the left hemisphere (recruitment of homologous regions within the left hemisphere) to complete the task, indicating an inefficient right hemisphere circuit. Alternatively, we thought that the NF-1 group might show an increased volume of activation in frontal regions and decreased volume of activation in posterior regions, representing an over-taxation of visuospatial working memory systems for task completion. A final possibility was that the NF-1 group could show an increased volume of activation in occipital lobe with reduced volume of parietal lobe activation, suggesting that areas important for more basic visual processing are taxed to a greater degree.

Methods

Participants

Twenty-six individuals, ages 7 to 15 years, participated in the study: 13 with NF-1 (6 females; mean age and SD: 9.80 ± 1.83) and 13 controls (6 females; 9.78 ± 2.56). Participant characteristics are shown in Table 1. Each parent gave written consent, while each child signed a separate assent statement, and procedures were carried out in accordance with the Johns Hopkins Medical Institutional Review Board.

Participants were excluded from participation if they were shown to have a clinically significant intracranial abnormality on MRI including traumatic brain injury (other than UBOs for children with NF-1), optic glioma, significant or uncorrectable hearing or vision loss, seizures, full-scale IQ less than 70, and major psychiatric illness. Participants either previously diagnosed with attention deficit hyperactivity disorder (ADHD) or met criteria from parent questionnaires (administered as part of this study) were included in the study, including those who were taking stimulant medications. Participants were not taken off stimulant medication as studies have shown that there is no effect on the blood-oxygen-level-dependent response measured by fMRI (Rao et al., 2000). Five out of the 26 participants (1 control, 4 NF-1) were receiving stimulant medication at the time of the study.

Participants for this study were part of a larger study comparing reading and visuospatial ability between children with NF-1, children with a history of a reading disability, and typically developing children. During their visit, participants were given a comprehensive battery of psychoeducational and academic achievement measures as well as tests measuring visuospatial ability (although selected tests are reported in the current study; see Table 1). Each individual received the Wechsler Intelligence Scale for Children—III (WISC-III; Wechsler, 1991) to determine eligibility based upon FSIQ criteria. For the NF-1 group, reading disability status was defined by scores on the Basic Reading subtest of the Wechsler Individual Achievement Test (WIAT; Wechsler, 1992) and the Word Attack subtest of the Woodcock Johnson Psychoeducational Battery—Revised (WJ-R; Woodcock & Johnson, 1989). Children in the NF-1 group who scored at or below the 25th percentile on both subtests were classified as reading disabled. All children in the control group scored at or above the 40th percentile on both subtests. Although a formal diagnosis of ADHD was not received, participants were characterized as qualifying for ADHD status by meeting criteria from two out of three of the following questionnaires filled out by parents: Achenbach Child Behavior Checklist—Parent Report Form (CBCL; Achenbach, 1991); Conners' Rating Scales-Revised (Conners, 1997); and the Attention Deficit Hyperactivity Rating Scale (DuPaul, 1991). To qualify on the CBCL, the T-score had to be equal to or greater than 65 on the Attention Problems index. For the Conners, a T-score equal to or greater than 65 was needed on either the DSM-IV Inattentive or the DSM-IV Hyperactive-Impulsive scale. To meet criterion for the DuPaul, either a percentile greater than or equal to 94 on the Inattentive or Hyperactivity indices was needed OR the presence of 6 out of 9 characteristics from these indices was needed.

Task Description

To examine differences in visuospatial processing between children with NF-1 and controls, we used an adapted version of the JLO (Benton et al., 1983; Kesler et al., 2004). The visuospatial task consisted of a fan of eleven lines displayed at the bottom of the screen; all of the lines were displayed in blue, except for two lines highlighted in yellow. Above the fan was a pair of yellow lines that were either oriented in the same position or were different as the two yellow lines highlighted in the fan. Participants pushed a button with their right index finger if the top two lines were oriented in the same position and pushed a button with their left index finger if the lines were oriented in different positions. The control task was a visual

discrimination task that controlled for basic visual discrimination abilities. During the visual discrimination task, participants looked at a fan of eleven blue lines displayed at the bottom of the screen; this time, above the fan was two lines that were either blue or yellow. Participants pressed the button with their right index finger when all the colors were the same and pressed the button with their left index finger when the colors were different.

For both the visuospatial and the visual discrimination tasks, there were six blocks each with each block consisting of 10 stimuli. Each stimulus presentation was 4 seconds with an inter-stimulus interval of 1 second. Two runs were presented with the total duration of each run approximately 5 minutes, 40 seconds. An LCD data projector projected the paradigm onto a rear-projection screen that participants viewed via a mirror fixed atop the MRI head coil. The paradigm was run through E-Prime (Psychology Software Tools, Pittsburgh, PA, USA) which also recorded the timing of both stimulus presentations and participant responses.

MRI procedure

Scanning was performed using a 1.5 Tesla ACS-NT Powertrack 6000 MRI scanner (Philips Medical Systems, Inc.) using body coil transmission and quadrature end-capped head coil reception. Functional MRI data were acquired using single shot echo planar imaging, with a 40 ms echo time (TE), 2.6 s repetition time (TR), 64×64 matrix, and 230 mm field of view (FOV), using 40 4.0 mm thick coronal slices with 0.5 mm inter-slice gaps, yielding a nominal acquisition voxel size of $(3.59 \times 3.59 \times 4.5)^3$, providing whole brain coverage.

Data Analysis

Post acquisition image processing and analysis was carried out using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>) on Matlab 6.1 (Mathworks, Inc., Natick, MA). Rec images from the scanner were converted to Analyze format, time corrected to adjust for within volume time of acquisition differences (Calhoun et al., 2000), and then coregistered. Due to the high incidence of macrocephaly in NF-1, which could result in between-subject variability in brain size, the data were not spatially normalized to a standard template. Task associated brain activation was assessed using a block design and statistical parametric maps were created corresponding with the time course associated with the visuospatial task compared to the baseline condition.

Region of interest (ROI) analyses were performed for each individual. The ROIs were identified using the Wake Forest University PickAtlas (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003; Maldjian et al., 2004). ROIs were chosen to correspond roughly to those found in the Billingsley et al. (2004) paper; however, additional divisions were made to look at differences within the parietal and occipital lobes. Thirteen regions were included in total. Frontal regions were subdivided into inferior frontal gyrus (BA 44/45), dorsolateral prefrontal cortex (BA 46), orbitofrontal cortex (BA 10/47), superior and middle frontal gyri (BA 8/9), and premotor cortex (BA 6). The temporal lobe ROIs corresponded to the inferior temporal gyrus, the middle temporal gyrus, and the superior temporal gyrus. Posterior regions included the inferior (BA 40) and superior (BA 7) parietal lobe as well as primary (BA 17), secondary (BA 18), and tertiary (BA 19) visual cortices. Furthermore, to control for potential differences due to total volume of activation, for each participant we divided each ROI by their total activation. Additionally, a square root transformation was applied to all proportional ROI data in order to obtain normalized distributions.

To look for differences between groups, several $2 \text{ (groups)} \times 2 \text{ (hemisphere)} \times \text{ROI}$ (proportional voxel count from each ROI; grouped by anatomical location by lobe) repeated measures multivariate analysis of variance (MANOVA) were performed. Additional analyses looking at frontal versus posterior regions between groups were also conducted to test for

potential differences in utilization between these areas. Furthermore, MANCOVAs were conducted controlling for age and FSIQ separately. Lastly, correlations were conducted with both in-scanner (accuracy and mean reaction time) and out-of-scanner (Benton's JLO) behavioral performance across ROIs to examine significant patterns of activation.

Results

Demographic Characteristics

A MANOVA was conducted to look for differences between groups on all demographic characteristics, including age/grade, FSIQ, and all academic/psychoeducational and visuospatial measures collected. Overall, there were no significant differences between NF-1 participants and control participants on age ($P < 0.621$) and grade ($P < 0.826$). However, the NF-1 group had a significantly lower Full scale IQ ($P < 0.007$) than the control group. For the visuospatial measures, the NF-1 group performed significantly worse than the control group on Benton's Judgment of Line Orientation ($P < 0.029$) and both the Position and Space ($P < 0.017$) and Visual Closure ($P < 0.002$) subtests from the DTVP-2; however, there was not a significant difference between groups on the Hooper Visual Organization Test ($P < 0.255$). There were significant differences between the groups on all of the academic achievement measures except for the Listening Comprehension subtest ($P < 0.447$), with the NF-1 group performing more poorly than the control group: Basic Reading ($P < 0.000$), Reading Comprehension ($P < 0.006$), and Word Attack ($P < 0.000$). Eight of the NF-1 participants met criterion for reading disability on a combination of the Basic Reading and Word Attack subtests. None of the control participants met criteria for a reading disability. Seven of the NF-1 participants and five of the control participants met criteria for ADHD diagnosis based off parent behavioral questionnaires.

During the MRI session, both the control participants and participants with NF-1 received T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences to examine whether UBOs existed. Trained radiologists at the Johns Hopkins Hospital read the T2-weighted and FLAIR scans; but no formal measurements of UBO volumes were conducted. Eight of the 13 participants with NF-1 had one or more UBOs that were visible on both MRI images, while none of the control participants had any evidence of a UBO. Two out of the eight NF-1 participants had only one UBO, two out of eight had two UBOs (typically bilaterally in one region), while four out of the eight had three or more UBOs in multiple areas. Across all participants, no one had a UBO in the regions of interest that were included in the analyses.

fMRI Behavioral Results

Overall, control children had a mean accuracy of $80.8\% \pm 12.9\%$ and 1720.72 ± 194.57 mean reaction time while children with NF-1 had a mean accuracy of $71.6\% \pm 14.1\%$ and 1614.69 ± 301.62 mean reaction time. Results of two-sample *t*-tests revealed that there were no significant differences between groups on performance ($P = 0.096$) and response time ($P = 0.297$).

ROI Results

Frontal Regions—All square-root transformed-proportional values for each ROI can be found in Table 2. Within the frontal lobe, a significant main effect of ROI was found ($T = 6.690$, $F = 35.125$, $df = 4, 21$, $P < 0.000$) indicating that there were differences between ROIs when collapsed across groups; post-hoc tests determined that all of the ROIs were significantly different from each other with the exception of BA 47/10 versus BA 8/9. There was a significant Side $\times$ Group interaction ($T = 0.431$, $F = 10.356$, $df = 1, 24$, $P < 0.004$), with post-hoc analyses indicating that NF-1 participants had significantly more left than right hemisphere activation while controls had significantly greater right than left hemisphere activation. Additionally,

there was also a significant Side $\times$ ROI $\times$ Group interaction ($T = 0.578$, $F = 3.035$, $df = 4, 21$, $P < 0.040$). Subsequent analyses for each ROI confirmed that control participants had significantly greater volume of activation in right BA 44/45 ($P < 0.013$) and a marginally significant greater volume of activation in right BA 8/9 ($P < 0.069$) when compared to the NF-1 group (see Figure 1). When controlling for age, there was no longer a main effect for ROI, but both interactions remained significant. When controlling for FSIQ there was no longer a main effect of ROI and the Side $\times$ ROI and Side $\times$ ROI $\times$ Group interactions were also not significant; however, a main effect of Side as well as ROI $\times$ Group interaction became significant. Post-hoc analyses indicated that control participants had marginally significant greater activation than NF-1 participants in BA 44/45 ($P < 0.070$) while there were no other significant differences across the other frontal ROIs.

Temporal Regions—Within the temporal lobe, a significant main effect of ROI was found ($T = 3.460$, $F = 39.794$, $df = 2, 23$, $P < 0.000$), with post-hoc analyses indicating that all the ROIs were significantly different from each other. There was also a marginally significant main effect of Side ($T = 0.161$, $F = 3.870$, $df = 1, 24$, $P < 0.061$) signifying a trend towards greater activation in the right hemisphere of the temporal lobe. For the analyses that controlled for age, as well as those that controlled for FSIQ, the main effect of ROI remained significant while the main effect of Side was not significant.

Posterior Regions—A significant main effect of ROI was found in parietal regions ($T = 1.489$, $F = 35.742$, $df = 1, 24$, $P < 0.000$), and post-hoc analyses indicated that BA 7 was used significantly more than BA 40 across groups. There was a significant Side $\times$ Group interaction ($T = 0.308$, $F = 7.399$, $df = 1, 24$, $P < 0.012$), with post-hoc analyses revealing that NF-1 participants having significantly more left than right hemisphere activation across ROIs. When controlling for age, the main effect of Side was not significant, but the Side $\times$ Group interaction remained significant. When controlling for FSIQ, there was no longer a main effect of ROI or a significant Side $\times$ Group interaction. Within the occipital lobe, there was a significant main effect of ROI ($T = 5.727$, $F = 65.855$, $df = 2, 23$, $P < 0.000$), with post-hoc analyses indicating that all the ROIs were significantly different from one another. Additionally, there was a marginally significant Side $\times$ ROI interaction ($T = 0.280$, $F = 3.223$, $df = 2, 23$, $P < 0.058$), with homologous regions showing similar levels of activation, but all other ROIs showing significantly different amounts of activation from each other. There was also a significant Side $\times$ ROI $\times$ Group interaction ($T = 0.797$, $F = 9.165$, $df = 2, 23$, $P < 0.001$); subsequent analyses confirmed that control participants had a marginally significantly greater volume of activation in left BA 17 ($P < 0.052$) when compared to NF-1 participants (see Figure 2). For the analyses that controlled for age, as well as for those analyses that controlled for FSIQ, there was no longer a main effect of ROI, nor was there a significant Side $\times$ ROI interaction; however, the significant Side $\times$ ROI $\times$ Group interaction remained.

Frontal vs. Posterior Regions—For this analysis, all frontal regions were included; however, for the posterior regions, the temporal lobe was not included since the primary regions of interest consisted of the parietal and occipital lobes. When comparing the volume of activation between frontal regions and posterior regions across groups, a significant main effect of frontal to posterior was found ($T = 0.377$, $F = 9.055$, $df = 1, 24$, $P < 0.006$) indicating that, in general, participants showed an increased volume of posterior activation as compared to frontal activation. A significant Side $\times$ Group interaction ($T = 0.428$, $F = 10.267$, $df = 1, 24$, $P < 0.004$) revealed that NF-1 participants showed significantly more left than right hemisphere activation while controls showed significantly greater volume of activation in the right hemisphere than in the left hemisphere. Additionally, there was a marginally significant Side $\times$ Group $\times$ Direction interaction ($T = 0.173$, $F = 4.149$, $df = 1, 24$, $P < 0.053$), but subsequent post-hoc analyses indicated no specific significant differences amongst the ROIs. When

controlling for age, there was no longer a significant main effect of direction; however, the Side $\times$ Group interaction and marginally significant Side $\times$ Group $\times$ Direction interaction remained. When controlling for FSIQ, there was no longer a main effect of Direction and the Side $\times$ Group $\times$ Direction interaction was also not significant; however, the Side $\times$ Group interaction was marginally significant and a Direction $\times$ Side interaction emerged.

Correlations—Significant positive correlations across ROIs for Benton's JLO were seen in bilateral inferior temporal gyrus and occipital lobe. Additional significant positive correlations were seen in right hemisphere regions including all frontal ROIs and parietal ROIs (marginally significant in superior parietal lobe-BA 7). For in-scanner behavioral correlations, there were no significant correlations with mean reaction time; however, significant positive correlations were seen for accuracy in bilateral inferior temporal gyrus, occipital (BA 17/18/19), and parietal lobes (BA 7/40) as well as right premotor and dorsolateral prefrontal cortex (BA 6/8/9).

Discussion

Overall, participants activated regions that were consistent with previous neuroimaging findings of visuospatial processing (Kesler et al., 2004; Ng et al., 2001) showing substantial activation in posterior regions, including the parietal and occipital lobes, with additional activation present within frontal regions. This was also evidenced with both in-scanner and out-of-scanner behavioral performance. However, our results showed several differences between groups. Generally, participants with NF-1 showed different patterns of activation than controls. In particular, participants with NF-1 showed left greater than right hemisphere volume of activation across the frontal lobe and in posterior regions including parietal lobe and occipital cortices. In general, the control group showed greater right than left hemisphere activation primarily in frontal regions. Results of the frontal/posterior analysis confirmed that: 1) both groups had significantly greater volume of posterior activation compared to frontal activation and 2) the NF-1 group showed significantly greater left than right hemisphere activation while the control group had significantly greater right than left hemisphere activation. On the whole, results remained relatively the same when controlling for age and FSIQ, suggesting that findings can not be attributed to developmental patterns or general ability.

Generally, our results support the hypothesis that individuals with NF-1 have problems with visuospatial processing due to an inefficient right hemisphere network. This was evidenced by recruitment of homologous left hemisphere regions for task completion, particularly in frontal, parietal, and occipital regions, areas thought to be important for visuospatial processing. This finding was also coupled with relative underactivation in right frontal regions. Nevertheless, our results do not seem to suggest that the problems are due to over-taxation of either visuospatial working memory or basic visual processing. Although we predicted that we would see additional frontal recruitment, it was not due to underactivation in posterior regions, as hypothesized. Thus, we were not able to confirm that task completion was dependent upon over-utilization of visuospatial working memory systems. Additionally, our results do not support our third hypothesis that the NF-1 group might rely on basic visual processing to a greater degree exhibited by underactivation of parietal regions and overactivation of visual cortices. In fact, our results seem to contradict this hypothesis and show that there may actually be a deficit in basic visual processing in individuals with NF-1 compared to controls based upon relative underactivation of occipital cortices.

Interestingly, in contrast to the findings of Billingsley et al. (2004) that showed increased activation in medial occipital cortices, results of this study found a *reduction* of activation in primary visual cortex (see Figure 3). Billingsley et al. attributed the greater activity of posterior cortices relative to frontal cortices to a deficit in visuospatial processing, as poorer performance in their NF-1 group showed higher signal change in these areas. However, the regions that were

associated with medial occipital cortex in the Billingsley study correlated with our secondary visual cortex (BA 18) and superior parietal lobe (BA 7), with primary visual cortex activation not measured. Therefore, it is possible that participants with NF-1 in the Billingsley study had decreased magnitude of activation and lower signal change in primary visual cortex. It should also be noted that it may be somewhat difficult to compare results from the present study to Billingsley et al. due to differences across tasks in cognitive load. Future work is needed to explore differences across tasks, as well as whether there are in fact differences in neuronal activity, specifically, in primary visual cortex and, generally, throughout the entire optic pathway and the relationship with optic gliomas. It is important to investigate differences in the optic pathway and primary visual cortex in individuals with NF-1 as it may yield additional information about basic visual processing and whether there is a predisposition for abnormalities in processing of basic visual perception processing. To this end, usage of multiple methodologies to further identify/describe any differences at a more basic level of visual functioning (e.g., oculomotor studies, retinotopic mapping, ERP, etc.) will be especially useful to help pinpoint any abnormalities. If individuals with NF-1 *do* have deficits in basic visual skills, then interventions could be tailored appropriately so that optimal results could be obtained not only for visuospatial deficits, but also for other types of learning difficulties (e.g., reading difficulties).

One potential limitation of this study is the differences in reading ability across groups, with the NF-1 group having participants who met criteria for a reading disability. Levine et al. (2006) showed that even though children with NF-1 exhibited the “typical” RD characteristics of poor phonological processing, there was also an association between reading ability and visuospatial processing in individuals with NF-1 (that was not as present in individuals with RD from the general population). Nevertheless, although visuospatial processing has not been shown to be the primary influence in RD, it should be noted that some studies have found relationships between visuospatial processing and RD (e.g., Eden et al., 1996); these studies suggest that visuospatial processing is linked to reading disability. Although the contribution of visuospatial processing to reading is likely a minor explanatory variable for those in general population, the contribution of visuospatial processing to reading *may* be more relevant for individuals with NF-1, indicative of a more basic phenomenon below the level of type of cognitive integration required for phonological processing. Future studies are needed to investigate the interrelationships between reading ability and visuospatial processing in individuals with NF-1 by conducting studies that include control, pure RD without NF-1, NF-1 only, and NF-1 with RD samples.¹ This approach could help disentangle potential differences between groups as well as to clarify the characteristics attributable to NF-1 specifically. Additionally, it could also help to identify patterns of recruitment (i.e., abnormal recruitment of the other hemisphere) across different types of tasks, including those designed to type other cognitive processes (aside from visuospatial processing). Another potential limitation of this study is that we are not able to compare directly the brains of individuals within our NF-1 group with our control group due to the normalization process that is needed to put the brains into a common space. Additional work is needed to examine the impact of warping the brains of individuals with NF-1 to a standard template (e.g., how much displacement there would be due to macrocephaly/megalencephaly and the impact of T2-weighted hyperintensities) and the creation of a standard NF-1 template. Finally, it will be important to incorporate the study of the impact of presence, number, location, and volume of UBOs on patterns of activation.

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¹This study design could also be extended to other types of learning disabilities in other academic domains (e.g., math).

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Figure 1.

Comparison of the square root transformations of the proportional volume of activation in bilateral frontal regions between children with NF-1 and controls. The * denotes a significant difference between groups in right BA 44/45 and right BA 8/9 with increased activation in Controls as compared to NF-1.

Figure 2.

Comparison of the square root transformations of the proportional volume of activation for bilateral occipital regions between children with NF-1 and controls. The * denotes a significant difference between groups in left BA 17. A significant decrease in activation is shown in the NF-1 group as compared to the control group.

Figure 3.
Illustrative example of greater activation in left primary visual cortex in a control participant compared to an individual with NF-1.

Table 1

Demographic characteristics

Group	NF-1	Control
Age Mean (SD)	9.8 (2.1)	9.4 (2.6)
Handedness	R: 11, L: 2	R: 11, L: 2
Education Mean (SD)	4.4 (2.4)	4.2 (2.6)
FSIQ Mean (SD) ^{1**}	90.5 (11.1)	102.5 (9.6)
Basic Reading Mean (Range) ^{2**}	90.1 (77 – 105)	112.9 (102 – 130)
Listening Comprehension Mean (Range) ²	95.3 (80 – 109)	98.2 (76 – 117)
Reading Comprehension Mean (Range) ^{2**}	91.9 (67 – 113)	106.4 (83 – 122)
Word Attack Mean (Range) ^{3**}	86.8 (75 – 112)	112.5 (92 – 131)
Benton's JLO Mean (SD) [*]	10.8 (5.5)	15.9 (5.8)
Hooper Visual Organizational Test Mean (SD)	21.9 (3.2)	23.3 (2.9)
Position and Space Mean (SD) ^{4*}	7.1 (2.1)	9.7 (3.0)
Visual Closure Mean (SD) ^{4**}	6.1 (2.6)	10.8 (4.1)

¹ FSIQ: full-scale intelligence quotient measured using Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991)

² reading subtests used from Wechsler Individual Achievement Test (WIAT; 1992)

³ Word Attack subtest from the Woodcock-Johnson Psycho-Educational Battery—Revised (WJ-R; 1989)

⁴ Developmental Test of Visual Perception-2 (DTVP-2; Hammill, Pearson, & Voress, 1993)

* indicates a significant difference between groups at $p < 0.05$

** indicates a significant difference between groups at $p < 0.01$

Table 2

Proportional Values for each ROI

	Control		NF	
	R	L	R	L
BA 44/45*	0.074	0.069	0.043	0.054
BA 46	0.097	0.076	0.064	0.084
BA 47/10	0.167	0.146	0.140	0.159
BA 8/9*	0.176	0.149	0.124	0.163
BA 6	0.191	0.170	0.180	0.204
ITG	0.146	0.119	0.113	0.113
MTG	0.230	0.165	0.180	0.177
STG	0.170	0.152	0.147	0.145
BA 7	0.211	0.193	0.181	0.203
BA 40	0.135	0.116	0.129	0.150
BA 17#	0.081	0.085	0.072	0.053
BA 18	0.172	0.201	0.161	0.155
BA 19	0.207	0.199	0.168	0.197

* indicates a significant difference between groups within the right hemisphere

# indicates a significant difference between groups within the left hemisphere