Functional Brain Activation by BDNF Genotype in Chronic Aphasia

Abstract submitted for poster presentation at the Clinical Aphasiology Conference 2019

Introduction

The brain-derived neurotrophic factor (BDNF) gene has been shown to be important for synaptic plasticity in animal models (Fritsch et al., 2010). A common single nucleotide polymorphism involving a switch from valine to methionine at codon position 66 (Val66Val to Val66Met/Met66Met) has been shown to result in 18-30% less activity-dependent secretion of BDNF (Egan et al., 2003). The presence of the Met allele has been associated with poorer performance on cognitive tasks, activity-related cortical plasticity, and decreased functional brain activation in healthy adults (Hariri et al., 2003; McHughen et al., 2010; Chen et al., 2016), and poorer functional recovery and decreased functional brain activation in stroke patients (Johansson, 2011; Kim et al., 2016). The effects of BDNF genotype on functional brain activation in aphasia remain to be thoroughly investigated.

Aims

We aimed to explore functional brain activation by BDNF genotype in individuals with chronic aphasia due to left hemisphere stroke. Based on studies on healthy individuals and the stroke population, we hypothesized that the presence of the Met allele of the BDNF gene is associated with reduced functional brain activation compared to individuals with the Val66Val variant.

Methods

We recruited 87 individuals with chronic stroke-induced aphasia (Table 1). Of those, 53 (61%) had typical BDNF genotype (Val66Val), while 34 (39%) had atypical BDNF genotype (Val66Met/Met66Met). Participants performed a naming task during fMRI scanning in which they were presented with 40 colored pictures of high-frequency nouns. For the purpose of establishing a baseline for the fMRI data analysis, 20 colored abstract pictures were shown at random among the real picture presentation. We utilized general linear modeling and a standard hemodynamic response function to generate contrast maps isolating brain activation related to naming. We then explored our hypotheses using two approaches to analyze the data: 1) We obtained the number of voxels where naming-related brain activation was significantly greater than zero (FWE=.05) for each group and compared across groups, 2) Average group-based contrast maps were compared using a two-sample t-test ($p<.001$, uncorrected). WAB-AQ was used as a covariate in all analyses. Neuropsychological testing was conducted to compare language impairment between BDNF genotype groups.

Results

Participants in the typical and atypical BDNF genotype groups presented with distributed cortical and subcortical lesions that covered the middle cerebral artery territory. Greatest lesion overlap was identified in the longitudinal fasciculus (MNI coordinates: -34x-36x28; Figure 1) in the typical genotype group and the longitudinal fasciculus (MNI: -36x-8x25) and the insula (MNI: -44x-9x3; Figure 2) in the atypical genotype group.

The overall activation pattern was similar across groups, with greatest intensity of activation present in the bilateral posterior temporal gyrus, pre- and postcentral gyrus, and the longitudinal fissure (Figure 3). We found that the number of activated voxels was greater in the typical genotype group compared to the atypical group at the whole brain level (98,500 vs. 28,630; $t(85)=18.63$, $p<.001$), in the left hemisphere (37,290 vs. 7,000; $t(85)=8.33$, $p<.001$), and in the right hemisphere (74,830 vs. 30,630; $t(85)=11.29$, $p<.001$; Figure 4).

A group-based comparison of the average contrast maps identified two distinct clusters where activation was greater in the typical compared to the atypical genotype group: Brodmann area 48 (BA

48; t=3.91, p<.001) and BA 19 (t=3.34, p=.001). On the contrary, no area had greater activation in the atypical compared to the typical group (Table 2 and Figure 5).

Corresponding to results from functional MRI data analysis, we observed clear differences in language impairment between the typical and atypical BDNF genotype groups (Table 3), where aphasia severity was significantly greater in the atypical compared to the typical group (WAB-R AQ: 54.3 vs. 64.2, p=.033; PNT: 52.8 vs. 74.7, p=.047).

Discussions

Our findings indicate that functional brain activation in chronic post-stroke aphasia patients is mediated by BDNF genotype. Correspondingly, we found clear differences in aphasia severity between the two groups. These results are consistent with findings in healthy individuals (Hariri et al., 2003; Kleim et al., 2006; McHughen et al., 2010) and the stroke population (Johansson, 2011; Kim et al., 2016), while contrasting some findings in studies examining the association between BNDF genotype and recovery in acute aphasia (e.g., De Boer et al., 2017; Mirowska-Guzel et al., 2013). As the current study included patients in the chronic phase of aphasia, and given the subtle effects of BDNF genotype on BDNF secretion (18-30% decrease), our results may suggest that the effects of genotype accumulate over time in the recovery process, enabling individuals with the typical genotype to experience greater recovery than their counterparts with the atypical genotype. While this conclusion requires validation through further research, knowledge on how genetic factors affect recovery may have great clinical implications into the future.

Citations

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Tables and Figures

	Typical BDNF genotype (Val66Val) N=53		**Atypical BDNF genotype (Val66Met, Met66Met) N=34**		**95% CI of the difference**	**Two-sided p-value**
Characteristic	Mean	SD	Mean	SD		
Age	59.6	11.2	57.7	10.9	(-2.9, 6.7)	.433
Time post stroke (mo)	44.0	38.7	34.5	36.9	(-6.9, 26.0)	.253
Education (y)	15.1	2.4	15.2	2.9	(-1.3, 1.0)	.834
Lesion size (cc)	121.4	73.2	142.2	88.4	(-57.2, 15.5)	.257
Exercise before stroke (days/week)	3.0	2.6	3.5	2.5	(-1.6, .6)	.388
Exercise now (days/week)	3.0	2.4	3.1	2.2	(-1.2, .9)	.802
NIHSS	5.1	3.2	6.3	3.8	(-2.7, .4)	.147

Table 1. Participant's biographical characteristics for the typical and atypical genotype groups.

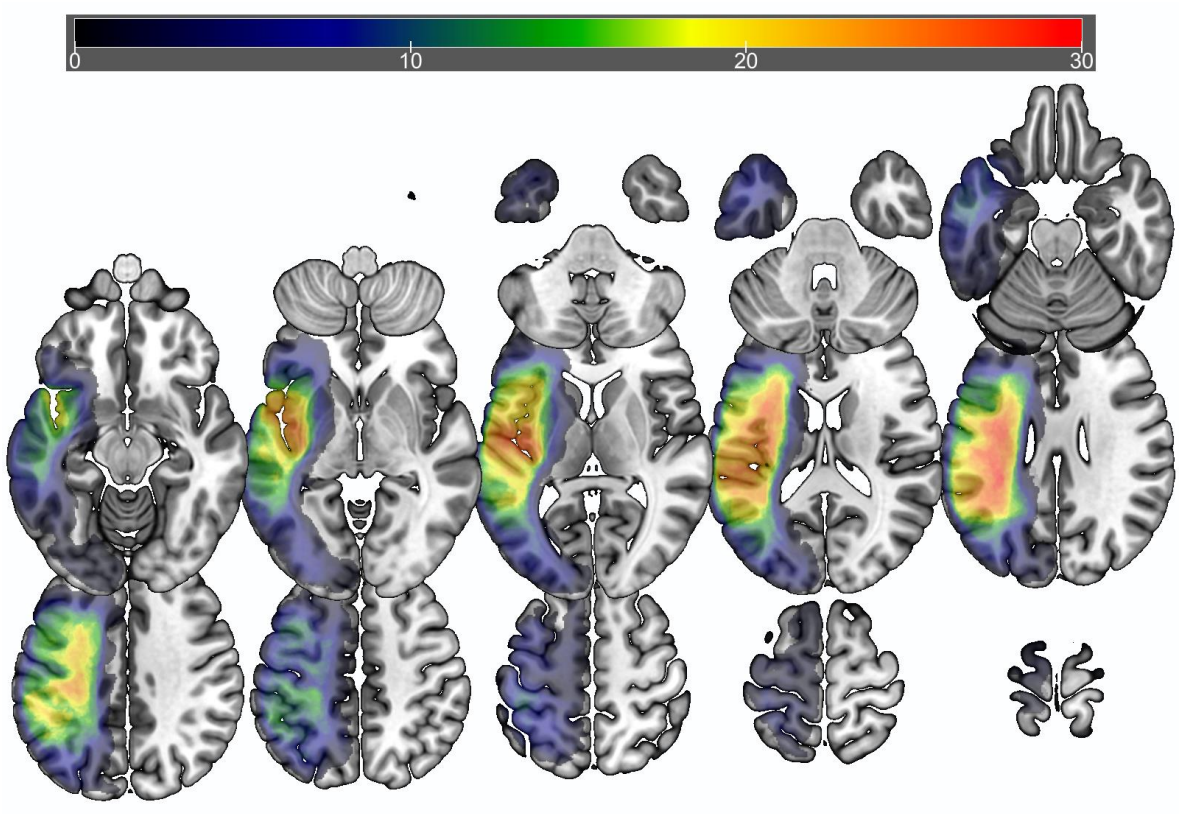

Figure 1. Lesion overlay map (n=53; maximum overlap n=39) showing lesion distribution of participants in the typical genotype group. Warmer colors indicate greater overlap.

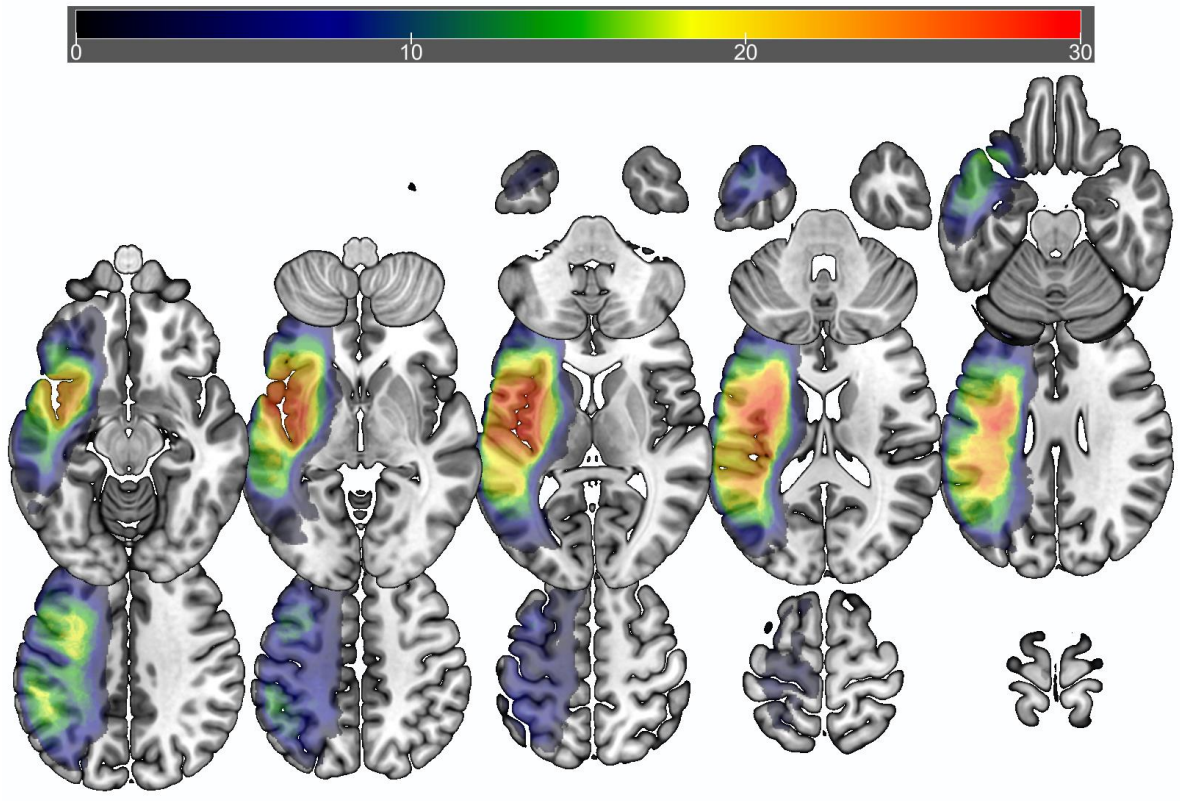

Figure 2. Lesion overlay map (n=34; maximum overlap n=29) showing lesion distribution of participants in the atypical genotype group. Warmer colors indicate greater overlap.

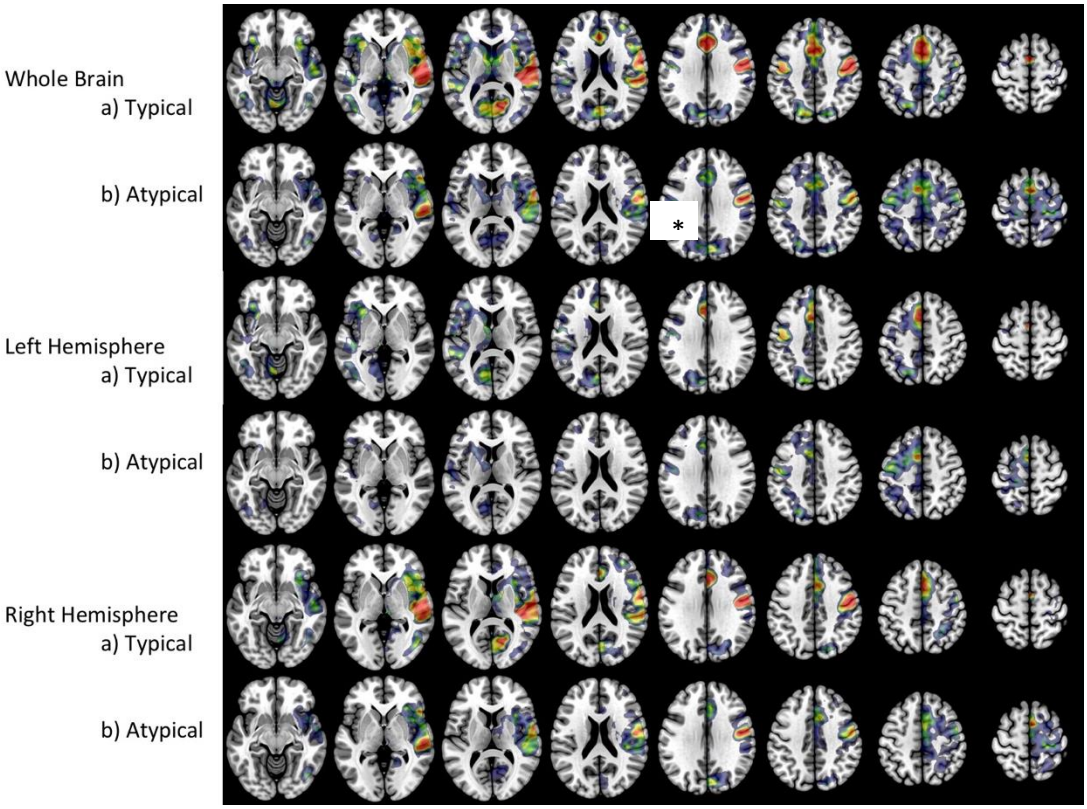

Figure 3. Significant activation during picture naming over abstract image viewing in the typical and atypical genotype groups. Warmer colors indicate greater activation intensity (t-value: 3.0-8.0).

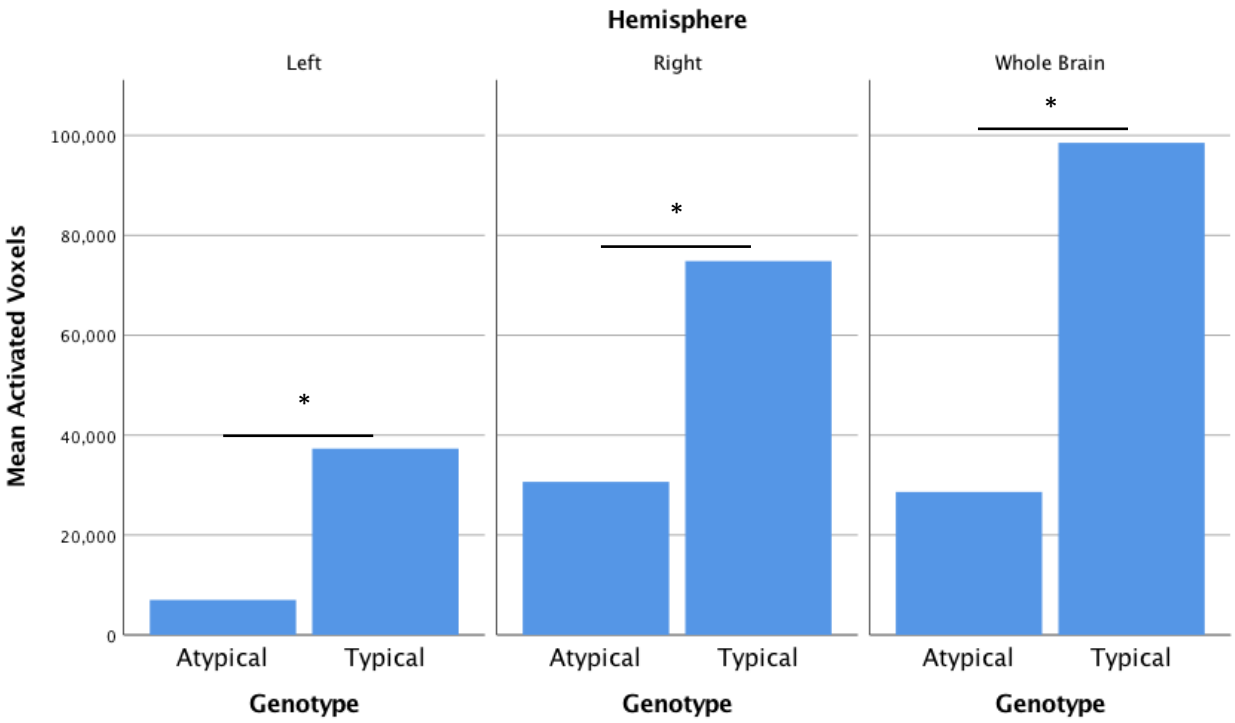

Figure 4. Number of activated voxels at the whole brain level and for the left and right hemispheres separately for the typical and atypical BDNF genotype groups. *p<.001.

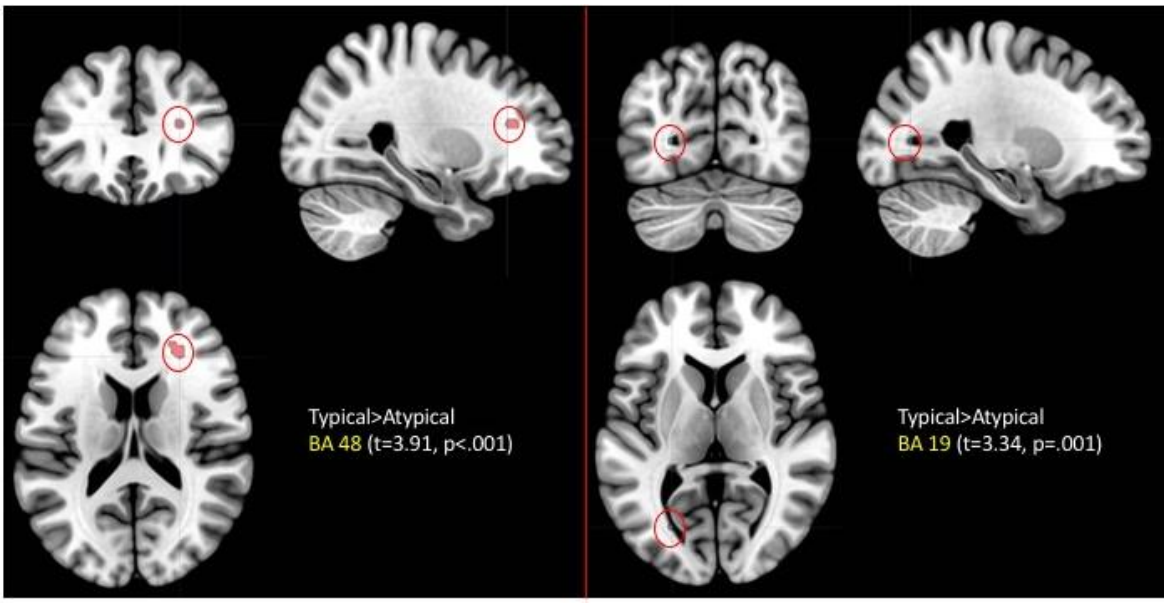

Figure 5. Areas showing significant difference in naming-related activation between the typical and atypical BDNF genotype groups at an uncorrected p-value of .001.

t-value	Cluster size (k_E)	x	y	z	Hemisphere	Location	p-value
Typical > Atypical							
3.91	16	26	36	16	Right	Medial frontal white matter (BA 48; subdivision of the cytoarchitecturally defined hippocampal region)	<.001
3.34	1	-26	-72	6	Left	Intracalcarine cortex (BA 19)	.001

Table 2. Clusters showing greater activation in the typical compared to the atypical BDNF genotype group.

	Typical BDNF genotype (val/val) N=53		**Atypical BDNF genotype (val/met, met/met) N=34**		**95% CI of the difference**	**Two-sided p-value**
Characteristic	Mean	SD	Mean	SD		
WAB-R AQ	64.2	20.3	54.3	21.0	(.81, 18.98)	.033
Spont. Sp.	12.2	4.4	10.4	4.6	(-.21, 3.75)	.079
Aud. Comp.	8.1	1.6	7.4	1.7	(.04, 1.49)	.040
Repetition	5.8	2.9	4.6	2.9	(-.10, 2.43)	.071
Naming	6.1	2.7	4.8	2.7	(.06, 2.44)	.040
Philadelphia Naming Test	74.7	51.1	52.8	43.3	(.26, 43.60)	.047
PPTT	45.7	4.2	46.2	4.6	(-2.47, 1.43)	.598
WAIS 3 Matrix Score	12.4	5.6	11.8	5.1	(-1.76, 2.87)	.635

Table 3. Results from behavioral testing on participants with typical and atypical BDNF genotype.