NeuroImage: Clinical 4 (2014) 444–453

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Increased topographical variability of task-related activation in perceptive and motor associative regions in adult autistics

Marie-Pier Poulin-Lord[a,b], Elise B. Barbeau[a,b,c], Isabelle Soulières[a,b,d], Oury Monchi[e,f], Julien Doyon[h], Habib Benali[g], Laurent Mottron[a,b,c,*]

[a]Centre d'Excellence en Troubles Envahissants du Développement de l'Université de Montréal (CETEDUM), Montréal, QC, Canada
[b]Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, QC, Canada
[c]Département de Psychiatrie, Université de Montréal, Montréal, QC, Canada
[d]Département de Psychologie, Université du Québec à Montréal, QC, Canada
[e]Centre de Recherche, Institut Universitaire de Gériatrie de Montréal, Montréal, QC, Canada
[f]Département de Radiologie, Université de Montréal, Montréal, QC, Canada
[g]Laboratoire d'Imagerie Fonctionnelle — U678, Faculté de Médecine, Pierre et Marie Curie — Pitié Salpétrière, Paris, France
[h]Département de Psychologie, Unité de Neuroimagerie Fonctionnelle (UNF), Université de Montréal, Montréal, QC, Canada

ARTICLE INFO

Article history:
Received 25 October 2013
Received in revised form 29 January 2014
Accepted 17 February 2014

Keywords:
Autism
fMRI
Plasticity
Primary areas
Associative areas

ABSTRACT

Background: An enhanced plasticity is suspected to play a role in various microstructural alterations, as well as in regional cortical reallocations observed in autism. Combined with multiple indications of enhanced perceptual functioning in autism, and indications of atypical motor functioning, enhanced plasticity predicts a superior variability in functional cortical allocation, predominant in perceptual and motor regions.

Method: To test this prediction, we scanned 23 autistics and 22 typical participants matched on age, FSIQ, Raven percentile scores and handedness during a visuo-motor imitation task. For each participant, the coordinates of the strongest task-related activation peak were extracted in the primary (Brodmann area 4) and supplementary (BA 6) motor cortex, the visuomotor superior parietal cortex (BA 7), and the primary (BA 17) and associative (BAs 18 + 19) visual areas. Mean signal changes for each ROI in both hemispheres, and the number of voxels composing the strongest activation cluster were individually extracted to compare intensity and size of the signal between groups. For each ROI, in each hemisphere, and for every participant, the distance from their respective group average was used as a variable of interest to determine group differences in localization variability using repeated measures ANOVAs. Between-group comparison of whole-brain activation was also performed.

Results: Both groups displayed a higher mean variability in the localization of activations in the associative areas compared to the primary visual or motor areas. However, despite this shared increased variability in associative cortices, a direct between-group comparison of the individual variability in localization of the activation revealed a significantly greater variability in the autistic group than in the typical group in the left visuo-motor superior parietal cortex (BA 7) and in the left associative visual areas (BAs 18 + 19).

Conclusion: Different and possibly unique strategies are used by each autistic individual. That enhanced variability in localization of activations in the autistic group is found in regions typically more variable in non-autistics raises the possibility that autism involves an enhancement and/or an alteration of typical plasticity mechanisms. The current study also highlights the necessity to verify, in fMRI studies involving autistic people, that hypoactivation at the group level does not result from each individual successfully completing a task using a unique brain allocation, even by comparison to his own group.

1. Introduction

Autism is characterized by social and communication alterations, as well as by repetitive behaviors and restrictive interests, combined with a large diversity among symptomatic profiles and individual developmental trajectories (American Psychiatric Association, 2013;

* Correspondence to: Laurent Mottron. Service de recherche, Hôpital Rivière-des-Prairies, 7070 Blvd. Perras, Montréal H1E 1A4, QC, Canada.
E-mail address: laurent.mottron@gmail.com (L. Mottron).

2213-1582/$ - see front matter © 2014 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/3.0/).
http://dx.doi.org/10.1016/j.nicl.2014.02.008

Newschaffer et al., 2007). The variability of autistic phenotype may result from the heterogeneity of environmental constraints and upbringing. However, mechanisms for heterogeneity may also be intrinsic to what autism is. The most obvious factor for phenotypic heterogeneity is the wide range of chromosomal regions and the several hundreds of polymorphisms that have been associated with autism (Scherer and Dawson, 2011). Whereas autism is understood as a final common pathway of these various mutations (Ben-David and Shifman, 2012), each genetic alteration may produce its own footprint on the phenotype. For instance, in the case of "syndromic autism", autism accompanied by tuberous sclerosis will differ from that accompanied by Fragile X. Another putative source of heterogeneity may be that the common effect of these mutations (either involved in syndromic or non-syndromic autism) is an increase in synaptic plasticity, a mechanism which may increase the experience-dependent variability in brain functional allocation (Markram and Markram, 2010; Mottron et al., 2013; Chung et al., 2012; Zoghbi and Bear, 2012). However, empirical arguments in favor of enhanced plasticity in autism are mostly indirect – based on examining in animal models the effect of genetic (Kelleher and Bear, 2008; Baudouin et al., 2012) or environmental (Markram and Markram, 2010) alterations – and mostly related to *microstructural* alterations (Markram and Markram, 2010).

Enhanced *functional* plasticity should also be present at the macroscopic level, and predict a greater variability in the autism group in regional allocation of brain functions (Barnes and Finnerty, 2010). Spatial variability in functional allocation is not identically distributed on the surface of the cortex. In an fMRI resting state study in typical individuals, Mueller et al. (2013) demonstrated that functional connectivity in hetero-modal association cortices (lateral prefrontal regions, temporo-parietal junction) is substantially more variable than that in unimodal perceptual and motor cortices. Regions of this increased inter-subject variability overlap with regions displaying more variable cortical folding, as well as with regions implicated in individual cognitive differences and regions displaying the largest evolutionary expansion between monkeys and humans. Autistics should therefore present more within-group variability in terms of functional allocation in associative regions, because these regions are intrinsically more variable and less genetically constrained in humans (Brun et al., 2009). There are indications that an autistic-specific plasticity process favors these regions, as manifested by their enhanced gyrification (Wallace et al., 2013), as well as by these regions being the primary locus of structural alterations, as revealed by the latest structural meta-analysis (Nickl-Jockschat et al., 2012). At the functional level, a recent ALE meta-analysis of 26 neuroimaging experiments using visual stimuli in autistic individuals revealed a material-specific functional reallocation of visual occipitoparietal associative areas, in the form of atypical spatial distribution of neural activity, and decreased activity in some frontal areas, in autistic relative to non-autistic individuals (Samson et al., 2012).

Pierce et al. (2001) were the first to report a greater individual variability in localization of cerebral activations in autistics. Whereas hypo-activation of the fusiform gyrus was observed in autistics at the group level during a face perception task, each autistic participant had a unique functional hot spot in response to faces (ranging from the frontal lobe to the occipital lobe and fusiform gyrus), while locations in non-autistics all fell within the fusiform face area. Similar increased inter-individual spatial variability in functional activations was also found in autistic groups during a visuomotor sequence learning task (Müller et al., 2003; Müller et al., 2004). In these studies, the 3D distance between the group's strongest activation peak in a specific region and each individual's closest peak was used as a direct measure of individual spatial variability. The premotor (BA 6) and the superior parietal (BA 7) cortices were used as target regions. Compared to typical individuals, autistics showed greater inter-individual spatial variability and decreased activation in the right superior parietal region (BA 7) during the early learning stage, and greater variability and activation in the right premotor region (BA 6) during the late learning stage. Scherf et al. (2010) used a similar computation of the individual variability in a study involving face, object and place processing. Greater variability in localization of activations was observed within the autistic group, but only in the fusiform gyrus during face processing. Whereas these findings are consistent with our hypothesis of enhanced variability, they are post-hoc findings, and do not compare primary and associative perceptual and motor regions. This distinction is of interest because the main difference in variability reported in typical individuals involves contrasting primary and associative regions (Mueller et al., 2013; Tahmasebi et al., 2012).

The aim of the study was to use functional magnetic resonance imaging (fMRI) to determine whether there is increased inter-individual variability in the localization, intensity and size of cerebral activations within the primary and associative areas of both visual and motor modalities in autistic individuals, compared to non-autistic individuals. Between-group comparisons of whole brain activations were also performed to determine if individual variability is associated with between-group differences in task-related activity. We distinguished primary and associative areas of visual and motor modalities recruited during a visuo-motor imitation task, using anatomical ROIs. An easy visuo-motor task was chosen in order to produce a combined activation of visual and motor cortices. BA 4 (primary motor cortex), BA 6 (premotor cortex and supplementary motor area, SMA), and BA 7 (visuomotor superior parietal cortex) were selected as ROI to investigate motor functions. BA 18 (V2: secondary visual cortex) and BA 19 (associative visual cortex) were grouped together to represent the global associative areas of the visual cortex, and BA 17 (V1: primary visual cortex) composed the visual ROI.

2. Methods

2.1. Participants

The initial experimental sample comprised 26 autistic participants and 23 typically developing participants recruited from the research database of the Université de Montréal Autism Center of Excellence at the Rivière-des-Prairies Hospital (Montreal, Canada). The autistic and non-autistic groups were matched on age, gender, Wechsler Full-scale and Performance IQ (WISC-III or WAIS III, Canadian norms), Raven's Progressive Matrices percentile (North American norms) (Raven, 1976) and manual preference estimated using the Edinburgh Handedness Inventory (Oldfield, 1971). Two left-handed autistics were not included in the analysis, in order to satisfy group matching in handedness. Most autistic participants were diagnosed using a multidisciplinary assessment that included a clinical evaluation based on DSM-IV criteria, the Autism Diagnostic Interview Revised (ADI-R) (Lord et al., 1994) and the Autistic Diagnostic Observation Schedule (ADOS-G modules 3–4) (Lord et al., 1989). However, some participants were characterized using expert interdisciplinary judgment only (one participant) or combined with either ADOS-G (two participants) or ADI-R (two participants). Typical participants were screened for personal or familial neurological or medical conditions known to affect brain function. Exclusion criteria were uncorrectable visual impairment, current use of psychoactive or vasoactive medications and use of drugs or alcohol exceeding 2 drinks per day. All structural scans were reviewed by a neurologist to ensure that no participant had any anatomical abnormalities. Written informed consent was obtained from all participants in accordance with the Regroupement Neuroimagerie/Québec IRB approved protocol 08-09-003. All participants received monetary compensation for their participation.

2.2. Stimuli and procedure

The visuomotor imitation task included 15 different hand gestures drawn in black and white, each illustrated twice to represent