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Research Report

Affected functional networks associated with sentence production in classic galactosemia

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ABSTRACT

Patients with the inherited metabolic disorder classic galactosemia have language production impairments in several planning stages. Here, we assessed potential deviations in recruitment and connectivity across brain areas responsible for language production that may explain these deficits. We used functional magnetic resonance imaging (fMRI) to study neural activity and connectivity while participants carried out a language production task. This study included 13 adolescent patients and 13 age- and gender-matched healthy controls. Participants passively watched or actively described an animated visual scene using two conditions, varying in syntactic complexity (single words versus a sentence). Results showed that patients recruited additional and more extensive brain regions during sentence production. Both groups showed modulations with syntactic complexity in left inferior frontal gyrus (IFG), a region associated with syntactic planning, and in right insula. In addition, patients showed a modulation with syntax in left superior temporal gyrus (STG), whereas the controls did not. Further, patients showed increased activity in right STG and right supplementary motor area (SMA). The functional connectivity data showed similar patterns, with more extensive connectivity with frontal and motor regions, and restricted and weaker connectivity with superior temporal regions. Patients also showed higher baseline cerebral blood flow (CBF) in right IFG and trends towards higher CBF in bilateral STG, SMA and the insula. Taken together, the data demonstrate that language

Abbreviations: (a)CBF, (absolute) cerebral blood flow; ASL, arterial spin labeling; BOLD signal, blood oxygenation level dependent signal; CAS, childhood apraxia of speech; EEG, electroencephalography; ERP, event-related potential; (f)MRI, (functional) magnetic resonance imaging; GALT, galactose-1-phosphate uridyl transferase; GLM, general linear model; IFG, inferior frontal gyrus; MTG, middle temporal gyrus; PG, precentral gyrus; POI, patch of interest; PT, planum temporale; SMA, supplementary motor area; STG, superior temporal gyrus; TE, echo time; TR, repetition time

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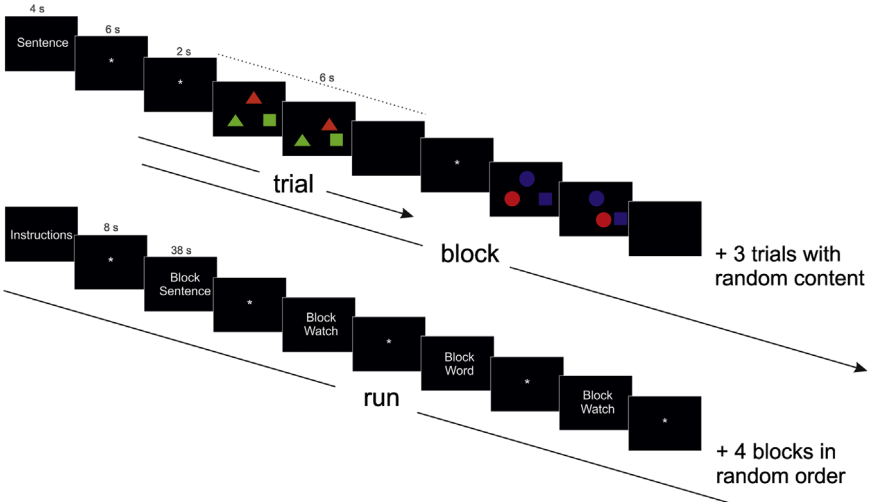
abnormalities in classic galactosemia are associated with specific changes within the language network. These changes point towards impairments related to both syntactic planning and speech motor planning in these patients.

1. Introduction

There is neuroscientific evidence for language production impairments in several planning stages in patients with classic galactosemia, an inborn error of galactose metabolism (Timmers et al., 2012). In the current study, we used functional magnetic resonance imaging (fMRI) to investigate potential deviations in functional neural networks involved in language production.

Classic galactosemia is a potentially lethal disorder that results from a profound deficiency of galactose-1-phosphate uridyl transferase (GALT) enzyme activity (Holton et al., 2001). After exposure to breast milk or a milk-based formula, infants suffer a rapid and devastating demise. Early dietary restriction of galactose prevents or resolves the acute manifestations of the disease. However, significant complications appear later in childhood involving the ovaries and the brain (Panis et al., 2004; Rubio-Gozalbo et al., 2010; Waggoner et al., 1990; Waisbren et al., 2012). Cognitive impairments include lower intelligence, memory impairments, slower information processing, as well as voice, motor (speech), and language impairments (Antshel et al., 2004; Doyle et al., 2010; Rubio-Agusti et al., 2013; Timmers et al., 2011; Widhalm et al., 2002). Childhood apraxia of speech (CAS) or verbal dyspraxia has traditionally been reported as an explanation for the speech and language impairments in galactosemia (Nelson et al., 1991; Robertson et al., 2000; Waggoner et al., 1990), although recent estimations indicate that only about 20–25% of the patients with galactosemia meet the criteria (Potter, 2011; Shriberg et al., 2011). In addition, patients with galactosemia have impairments in language planning (Potter et al., 2013). Vocabulary, grammar and word retrieval problems have been described (Schweitzer et al., 1993; Waggoner et al., 1990; Waisbren et al., 1983), as well as cases with clinically significant delays on pre-linguistic skills (at age 13 month) (Lewis et al., 2013), and failures to meet age-appropriate phonological awareness (aged 7–9) (Lewis et al., 2012). The majority of patients with galactosemia and history of speech sound disorders also have language disorders, which cannot be explained by lower cognitive abilities (Potter et al., 2008).



Description of the task

Language production	Sentence 'S'	*'The red triangle flies towards the green square.'*
	Word 'W'	*'triangle, red, square, green, to fly towards'*
Passive watching	Animated 'PA'	watch animated scene
	Static 'PS'	watch static scene (figures stay in start position)

Fig. 1 – Schematic overview of the language production task. Top: Contents of one block, starting with an instruction of the specific block condition (presented for 4 s), followed by a baseline period (6 s). Trials started with a baseline period (2 s), followed by the onset of the scene (animated plus freeze period; total duration of 4.5 s) and a blank screen (1.5 s). From the onset of the scene on, participants had 6 s to give their response. Total trial duration was 8 s, and total block duration (5 trials of same condition) was 60 s. Bottom: Contents of one run, starting with general instructions of the task and eight blocks – two per condition – preceded by a baseline period (10 s). One run had a duration of approximately 8 min. Further, the conditions and examples of responses are described.