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Grammar learning in older adults is linked to white matter microstructure and functional connectivity

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ABSTRACT

Age-related decline in cognitive function has been linked to alterations of white matter and functional brain connectivity. With regard to language, aging has been shown to be associated with impaired syntax processing, but the underlying structural and functional correlates are poorly understood. In the present study, we used an artificial grammar learning (AGL) task to determine the ability to extract grammatical rules from new material in healthy older adults. White matter microstructure and resting-state functional connectivity (FC) of task-relevant brain regions were assessed using multimodal magnetic resonance imaging (MRI). AGL performance correlated positively with fractional anisotropy (FA) underlying left and right Brodmann areas (BA) 44/45 and in tracts originating from left BA 44/45. An inverse relationship was found between task performance and FC of left and right BA 44/45, linking lower performance to stronger inter-hemispheric functional coupling. Our results suggest that white matter microstructure underlying specific prefrontal regions and their functional coupling affect acquisition of syntactic knowledge in the aging brain, offering further insight into mechanisms of functional decline in older adults.

1. Introduction

Even though certain aspects of language processing are frequently impaired in healthy older adults (e.g., Meinzer et al., 2009, 2012b; Tyler et al., 2010; Wingfield and Grossman, 2006), very few studies assessed the underlying neural substrates of these impairments. In particular, syntax is a fundamental feature of the human language faculty, important for communication in private and work-related contexts (Kaestle et al., 2001). In the context of the increasing proportion of elderly persons worldwide, age-related decline or preservation of syntactic processes has enormous relevance for individuals and for society. A better understanding of maladaptive or beneficial functional and structural neural changes enables the development of potential mechanism-driven techniques to improve functioning (e.g., using non-invasive brain stimulation, Flöel et al., 2011; Meinzer et al., 2012a).

Moreover, language impairments are among the earliest symptoms of age-associated pathological conditions like Alzheimer's disease and its precursors (Bickel et al., 2000; Henry et al., 2004; Murphy et al., 2006; Taler and Phillips, 2008) and are also core symptoms of post-stroke language impairments (aphasia; e.g., Meinzer et al., 2011). Given that patients suffering from degenerative diseases and stroke are usually older adults, the assessment of changes in language processing and their underlying neural substrates in healthy adults are highly relevant as they are the baseline from which these patients depart.

Age-related cognitive decline has been linked to structural alterations in cerebral white matter, and to changes in functional brain activity and connectivity patterns (for reviews see Goh, 2011; Madden et al., 2009; Park and Reuter-Lorenz, 2009). Previous studies have linked lower language performance in older adults to deterioration in bilateral white matter microstructure, as measured by fractional anisotropy (FA) using magnetic resonance imaging (MRI)-based diffusion tensor imaging (DTI; Obler et al., 2010; Stamatakis et al., 2011). For example, Obler et al. (2010) found that naming performance was correlated to FA values in left-hemisphere language-relevant brain regions as well as their right-hemisphere homologues. The authors concluded that successful naming skills of older adults may depend on white matter microstructure in brain regions and pathways in both hemispheres.

In line with findings in other cognitive domains (Park and Reuter-Lorenz, 2009) functional MRI (fMRI) studies that used language paradigms to compare local task-related activity patterns in young and older healthy adults frequently found more bilateral processing in the older groups as compared to a unilateral (left-lateralized) pattern in young adults (Meinzer et al., 2012b; Tyler et al., 2010; Wierenga et al., 2008). The behavioral relevance of age-related changes in the lateralization of task-related activity for cognition, and for language in particular, has not yet been conclusively established. Regarding non-linguistic tasks, some studies reported beneficial effects of additional activity in the hemisphere that is not-dominant for the task (e.g., Cabeza, 2002; Park and Reuter-Lorenz, 2009), while others interpreted their findings

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as the result of inefficient recruitment of specialized brain regions in the dominant hemisphere, disinhibition of non-specialized networks or enhanced demands placed on top-down control processes (e.g., Fling et al., 2011; Li and Lindenberger, 1999; Park and Reuter-Lorenz, 2009; Rajah and D'Esposito, 2005). In the language domain, beneficial effects of bilateral processing have primarily been reported for relatively easy tasks (Tyler et al., 2010; Wierenga et al., 2008) while it was associated with reduced performance during more challenging tasks (Meinzer et al., 2009, 2012b; Peelle et al., 2010). This would be in line with the assumption that control processes in left and/or right prefrontal areas can effectively compensate for structural damage or inefficient recruitment of specialized task-relevant neural populations to a certain degree (Davis et al., 2008; Park and Reuter-Lorenz, 2009). However, such "scaffolding" networks may be less efficient and prone to errors and at a higher level of challenge this may result in lower performance (cf. Park and Reuter-Lorenz, 2009, pp. 185–86).

More recently, researchers have also begun to explore changes in functional connectivity (FC) to assess potential age-associated changes in coordinated brain activity at the network level (Andrews-Hanna et al., 2007; Chen et al., 2009; Davis et al., 2011). In the language domain, however, only one recent study addressed cortical age-related changes at the functional network level. In this study, Peelle et al. (2010) found that reduced connectivity (i.e., co-variation between brain areas) within a mostly left-hemispheric syntax-processing network in older compared to young adults was associated with slower reaction times during a syntactic comprehension task.

To study the acquisition of novel syntactic knowledge, which is an important aspect of natural language learning (Forkstam et al., 2006; Petersson et al., 2004), the artificial grammar learning (AGL) task has proven to be effective (de Vries et al., 2008, 2009; Kürten et al., 2012). In this task, subjects are asked to memorize letter strings without being aware of their inherent grammatical structure (implicit acquisition period; Reber, 1967). Afterwards participants are presented with novel sequences and asked to decide whether those are in line with the implicitly learned syntactic structure. Structural and functional brain imaging as well as brain stimulation studies confirmed a crucial involvement of left Brodmann areas (BA) 44/45 in young adults during AGL paradigms (de Vries et al., 2009; Flöel et al., 2009; Forkstam et al., 2006; Petersson et al., 2004; Uddén et al., 2008). Forkstam et al. (2006) suggested a specific role of the left BA 44/45 in extraction of syntactic rules. AGL performance can further be divided in chunk-based (explicit; more superficial) and rule-based (implicit) learning performance. In chunk-based learning, participants learn fragments or so-called chunks of the training items, such as letter pairs or triplets (Perruchet and Pacteau, 1990). In rule-based learning, implicit learning of the rules underlying the artificial grammar, such as an 'M' may be followed by a 'V' after a variable number of 'S' (see Fig. 1 and Reber, 1967), have to be encoded in order to successfully classify novel letter strings as grammatical or non-grammatical. Notably, in young subjects, rule-based AGL performance was correlated with

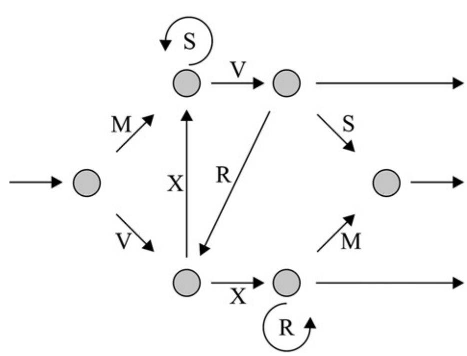

Fig. 1. Graphical representation of the finite state grammar used to generate the "grammatical" letter strings.

white matter microstructure underlying left but not right BA 44/45 and tracts originating from this area (Flöel et al., 2009). Furthermore, a significant age-related decline in performance has been shown for chunk-based but not rule-based learning elements representing explicit learning during AGL (Kürten et al., 2012; Meulemans and Van der Linden, 1997). The underlying neural correlates of inter-individual variability in older adults, however, have not been thoroughly scrutinized so far. In particular, previous studies have not combined structural and functional imaging to provide a comprehensive assessment of age-related changes in syntax processing. Therefore, in the present study we assessed AGL performance, as well as white matter microstructure and inter-hemispheric resting-state FC in 20 healthy older adults.

Based on the study by Flöel et al. (2009) that investigated white matter correlates of AGL in young adults, we hypothesized that higher AGL performance, particularly for chunk-based learning, would be associated with higher FA values in left BA 44/45 and in white matter pathways originating from this region in older adults as well. However, as a number of studies implicated right frontal involvement in language processing in older adults (Obler et al., 2010; Stamatakis et al., 2011), we also expected to find an association of performance with white matter underlying right BA 44/45.

Moreover, functional imaging and brain stimulation studies suggested that suppression of contralateral activity can benefit language and motor task performance (Schäfer et al., 2012; Thiel et al., 2006). In particular, in the context of highly lateralized functions like syntax processing (Friederici, 2011), performance may depend on successful inhibition of contralateral brain regions that are not involved in the respective task (Netz et al., 1995). Therefore, we also hypothesized that enhanced FC of specialized left-hemisphere regions (i.e., BA 44/45) with their right-hemisphere homologues, possibly mediated by reduced transcallosal or inter-hemispheric inhibition (Fling et al., 2011), would be associated with decreased behavioral performance.

2. Materials and methods

2.1. Participants

Twenty healthy elderly German speakers participated in the study (ten women; mean $\pm$ SD age: 69.9 $\pm$ 3.0 years, range: 64–76; years of education 16.3 $\pm$ 3.3 years, range: 11–22). Subjects were recruited from a local database of healthy older adults who underwent an extensive neuropsychological testing to assure normal cognitive functioning (working memory: digit span forward and backward (Wechsler, 1987), executive functioning: phonemic [letter S] and semantic [category animals] based fluency, and Trail-Making Test A and B (Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-Plus; www.memoryclinic.ch); verbal memory: Verbal Learning Memory Task (VLMT) (Helmstaedter et al., 2001)). Performance scores in neuropsychological tests were within age-corrected norms, see Table 1 for details. All participants were right-handed (Edinburgh Handedness Inventory (Oldfield, 1971)) and had no history of medical or neurological disorders. Data of one participant were not included in the analyses because he did not understand the task instruction (resulting in a d-prime $<$ 0, see below). Data of two participants had to be excluded either from DTI (n = 1) or resting state analyses (n = 1) due to severe movement artifacts, resulting in a total of 18 participants in each analysis and 17 in the linear regression model (see below). The study was approved by the local ethics committee. All subjects gave written informed consent and were reimbursed for their participation.

2.2. AGL task

The AGL task has been described in detail elsewhere (de Vries et al., 2009; Flöel et al., 2009; Kürten et al., 2012). In short, the task comprised two steps: (1) an acquisition part during which an artificial grammar