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Linking planning performance and gray matter density in mid-dorsolateral prefrontal cortex: Moderating effects of age and sex

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ABSTRACT

Planning of behavior relies on the integrity of the mid-dorsolateral prefrontal cortex (mid-dlPFC). Yet, only indirect evidence exists on the association of protracted maturation of dlPFC and continuing gains in planning performance post adolescence. Here, gray matter density of mid-dlPFC in young, healthy adults (18–32 years) was regressed onto performance on the Tower of London planning task while accounting for moderating effects of age and sex on this interrelation. Multiple regression analysis revealed an association of planning performance and mid-dlPFC gray matter density that was especially strong in late adolescence and early twenties. As expected, for males better planning performance was linked to reduced gray matter density of mid-dlPFC, possibly due to maturational processes such as synaptic pruning. Most surprisingly, females showed an inverted, positive interrelation of planning performance and mid-dlPFC gray matter density, indicating that sexually dimorphic development of dlPFC continues during early adulthood. Age and sex are hence important moderators of the link between planning performance and gray matter density in mid-dlPFC. Consequently, the assessment of moderator effects in regression designs can significantly enhance understanding of brain-behavior relationships.

Introduction

Successful completion of deliberate behavior beyond everyday routine relies on the ability to identify and select an appropriate sequence of actions before their actual execution. This ability to plan ahead future actions encompasses the mental conception and evaluation of several behavioral alternatives and their associated consequences (Goel, 2002; Ward and Morris, 2005). As one of the highest human cognitive abilities, it depends on the integrity of the prefrontal cortex (Owen, 2005). In particular, the functional contributions of the mid-dorsolateral part of the prefrontal cortex (mid-dlPFC) that refers to Brodmann areas 46 and 9/46 in middle frontal gyrus have been implicated to play a major role in planning and organization of behavior (e.g., Petrides, 2005; Unterrainer and Owen, 2006). Assessment of planning ability often employs disc-transfer paradigms such as the Tower of London task that was originally developed to examine planning impairments in patients with frontal lesions (Shallice, 1982). In this task, planning is required for an efficient transformation of a given start state into a predetermined goal state within the minimum number of moves (Berg and Byrd, 2002; Kaller et al., 2011a; for an illustration, see Fig. 1).

Previous developmental studies on the Tower of London task documented age-related improvements in planning ability from preschool age to adolescence (e.g., Asato et al., 2006; Huizinga et al., 2006; Kaller et al., 2008; Krikorian et al., 1994; Levin et al., 1991; Luciana and Nelson, 1998; Luciana and Nelson, 2002; Luciana et al., 2009). In a recent multi-center study employing an exceptionally large sample (n = 890, ranging from 10 to 30 years) and also more complex and demanding Tower of London problems with up to seven moves, Albert and Steinberg (2011) revealed that the developmental progress in planning ability extends beyond adolescence well into the mid-twenties (see also De Luca et al., 2003). In close parallel, mid-dlPFC is reported to manifest a likewise protracted course in its ontogenetic maturation that seemingly echoes its late evolvement during phylogenesis (Gogtay et al., 2004): Post-mortem investigations revealed not only a delayed synaptogenesis for middle frontal gyrus during early childhood, but also a considerable protraction in synapse elimination during adolescence (Huttenlocher and Dabholkar, 1997). In-vivo neuroimaging studies further showed that, compared to adjacent structures in more anterior and posterior parts of prefrontal cortex, mid-dlPFC reaches its maximum cortical thickness at a later age during

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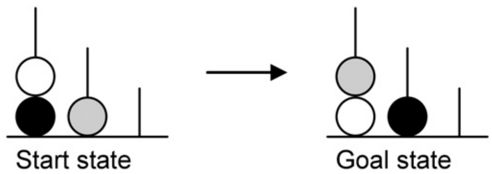

Fig. 1. Illustration of the Tower of London planning task. The aim of the task is to transform a given start state into a given goal state within the minimum number of moves. In the present example, an optimal solution can be accomplished within five moves.

childhood and is even one of the latest peaking regions in the entire human brain (Gogtay et al., 2004; Shaw et al., 2008). Moreover, subsequent reduction in gray matter density particularly in dorsal parts of frontal cortex proceeds well into the post-adolescent mid-twenties (Sowell et al., 1999; Sowell et al., 2001), possibly reflecting anatomical refinements of neuronal processing via synaptic pruning and the elimination of excess connections (Giedd, 2004; Gogtay et al., 2004; but see also Paus, 2005). In this regard, a recent study on post-mortem brain tissue confirmed that elimination of synaptic spines in dlPFC continues throughout the third decade of life (Petanjek et al., 2011).

Based on this apparent coincidence between (i) the prolongated cognitive development of planning ability and (ii) the protracted brain maturation in (mid-)dorsolateral prefrontal cortex that both extend well into adulthood, Albert and Steinberg (2011) suggested a direct link between these two processes. However, although intriguing and in line with extant views on the development of prefrontal function (e.g., Blakemore and Choudhury, 2006; Casey et al., 2005; Diamond, 2002; Paus, 2005), the specific link for planning ability has not been established in anatomical data so far.

In the present study, we therefore investigated the relationship between gray matter density in mid-dlPFC and planning ability in a larger sample of late adolescents and young adults (18–32 years). Region-of-interest (ROI) analyses were based on functionally defined locations of left and right mid-dlPFC derived from a previous experiment employing the Tower of London task in combination with functional magnetic resonance imaging (Kaller et al., 2011b). Given that the parallel of developmental changes in morphology and cognitive ability further suggests a moderating effect of age on the presumed brain-behavior relationship (also see below), multiple regression analysis with interaction effects was applied (cf. Cohen et al., 2003; Jaccard and Turrisi, 2003). Moreover, putative sex-related differences in Tower of London performance remain a matter of contention (e.g., Boghi et al., 2006; De Luca et al., 2003; Unterrainer et al., 2005), while sexual dimorphisms in brain development and resultant morphological organization are commonly known (e.g., Allen et al., 2003; Giedd et al., 1999; Goldstein et al., 2001; Gur et al., 2002; Lenroot et al., 2007). Hence, besides age, sex was added as another moderator to account for potential sex-related variability in the relationship between planning performance and gray matter density in mid-dlPFC.

Methods

Subjects

Present analyses were based on two previously acquired data sets (incl. pilots) that both comprised the administration of an identical problem set of the Tower of London planning task as well as the acquisition of anatomical data using an identical imaging protocol on the same magnetic resonance imaging (MRI) scanner. In the first study (Kaller et al., in press), general planning ability was initially assessed with a standard four- to six-move Tower of London problem set as means for controlled assignment of subjects to different experimental groups, that were then tested using a different variant of the task during transcranial magnetic stimulation (TMS). Only data of the initial testing with the original Tower of London were included in the present analyses, along with anatomical MRI scans acquired for neuronavigated application of stimulation over mid-dlPFC. The sample included here (Sample 1, n = 59, 26 female; age M = 24.24 years, SD = 2.51; all right-handed) comprised the resulting data sets after exclusion of two subjects that had been also excluded in the study of Kaller et al. (in press) either due to an incidental finding in the anatomical MRI scan or severely poor performance in the initial assessment of global planning ability. Contrary to the data set of Kaller et al. (in press), the current sample included a TMS pilot subject who was pre-tested but then stimulated using a different TMS protocol. In addition, the present sample set included six data sets that had been discarded in the TMS study due to events during the TMS session (technical malfunctions, safety reasons, non-compliant behavior, outlier), as these reasons were unrelated to the initial assessments of global planning ability considered here.

In the second study (Kaller et al., 2012), psychometric properties of an extended version of the same standard Tower of London problem set were assessed. Due to participation in other imaging studies, anatomical MRI scans were available for a subgroup of this study's subjects (Sample 2, n = 45, 19 female; age M = 23.56 years, SD = 2.76; all right-handed). Given that (i) the subjects included from these two sources showed a virtually identical planning accuracy in terms of proportions of problems perfectly solved in the minimum number of moves (Sample 1, M = 72.67%, SD = 9.83; Sample 2, M = 71.34%, SD = 11.67; $t_{(102)} = .607$, $p = .545$) and that (ii) they also did not differ with respect to age ($t_{(102)} = 1.324$, $p = .188$) or sex ($\chi^2 = .035$, $df = 1$, $p = .851$), the two data sets were collapsed in the subsequent analyses (for additional assessments of the data sets' comparability, see also Tower of London task section).

In total, data of 104 subjects were included in the present analyses (45 female). Subjects were aged between 18 and 32 years (M = 23.95 years, SD = 2.63). All subjects were right-handed and had normal or corrected-to-normal visual acuity. None of them was under medical treatment or reported a history of psychiatric or neurological illness. In both primary studies on the Tower of London task, written informed consent was obtained prior to participation (cf. Kaller et al., in press, 2012). In addition, acquisition of anatomical images was approved by local ethics authorities. Subjects received monetary compensation for their participation (approximately 10 €/h).

Tower of London task

The Tower of London task (Shallice, 1982) is a frequently used neuropsychological test instrument for assessing planning ability in various clinical and healthy populations (Kaller et al., 2011a). In its original version, three balls of different colors are placed on three different rods of different lengths (Berg and Byrd, 2002). Subjects are presented with a start state and are instructed to transform it into a given goal state. In order to solve the problem in the least possible number of moves, subjects are thus requested to plan ahead a solution before manually executing the moves. Three rules have to be followed: (i) Only one ball can be moved at a time, (ii) balls must not be placed outside the tower, and (iii) if more than one ball is stacked on a rod, only the topmost ball can be moved.

The Tower of London problem set applied in the two primary studies consisted of an optimized problem selection recently suggested by Kaller et al., (2011a). In its extended version this problem set comprises eight four-, five-, six-, and seven-move problems each that instantiate a linear increase of problem difficulty (see Kaller et al., 2012, for detailed psychometric evaluations). For the present analysis, however, only four-, five- and six-move problems were considered because subjects in Sample 1 were not assessed with seven-move problems (cf. Kaller et al., in press).

In both samples, subjects were tested individually in quiet laboratory rooms and administered a computerized version of the original Tower of