A Meta-Analysis on the Neural Basis of Planning: Activation Likelihood Estimation of Functional Brain Imaging Results in the Tower of London Task

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Abstract: The ability to mentally design and evaluate series of future actions has often been studied in terms of planning abilities, commonly using well-structured laboratory tasks like the Tower of London (ToL). Despite a wealth of studies, findings on the specific localization of planning processes within prefrontal cortex (PFC) and on the hemispheric lateralization are equivocal. Here, we address this issue by integrating evidence from two different sources of data: First, we provide a systematic overview of the existing lesion data on planning in the ToL (10 studies, 211 patients) which does not indicate any evidence for a general lateralization of planning processes in (pre)frontal cortex. Second, we report a quantitative meta-analysis with activation likelihood estimation based on 31 functional neuroimaging datasets on the ToL. Separate meta-analyses of the activation patterns reported for *Overall Planning* (537 participants) and for *Planning Complexity* (182 participants) congruently show bilateral contributions of mid-dorsolateral PFC, frontal eye fields, supplementary motor area, precuneus, caudate, anterior insula, and inferior parietal cortex in addition to a left-lateralized involvement of rostralateral PFC. In contrast to previous attributions of planning-related brain activity to the entire dorsolateral prefrontal cortex (dlPFC) and either its left or right homolog derived from

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single studies on the ToL, the present meta-analyses stress the pivotal role specifically of the mid-dorsolateral part of PFC (mid-dlPFC), presumably corresponding to Brodmann Areas 46 and 9/46, and strongly argue for a bilateral rather than lateralized involvement of the dlPFC in planning in the ToL. *Hum Brain Mapp* 38:396–413, 2017. © 2016 Wiley Periodicals, Inc.

Key words: prefrontal cortex; planning; lesion studies; functional neuroimaging; meta-analysis; activation likelihood estimation; Tower of London Task

INTRODUCTION

The functional anatomy of planning processes in the prefrontal cortex (PFC) and the concomitant question of hemispheric lateralization have been a matter of interest since the seminal study of Shallice [1982] on the Tower of London (ToL) task. In that study, patients with left anterior brain lesions were found to have substantial decrements in planning accuracy and increased initial thinking times when compared to patients with right anterior lesions as well as with left and right posterior lesions [Shallice, 1982]. Lateralization of planning processes in the ToL was thereafter addressed in several neuropsychological studies with brain-lesioned patients. But as summarized in Box 1, effects of lateralization of (pre)frontal lesions on planning accuracy (in terms of optimal solutions within the minimum number of moves) and initial thinking times could not be found in any of these subsequent studies (Table B1) [see also Sullivan et al., 2009].

However, effects of prefrontal lateralization may have been attenuated in lesion studies due to several methodological reasons: The number of lesion studies on the topic is small and their sample sizes are mostly limited as well. Furthermore, there is commonly a high variability in extent, localization, and focality of lesions in PFC and beyond, as well as a high variability in functional impairments given heterogeneous etiologies and time courses of brain plasticity and reorganization following brain injuries [cf., Rorden and Karnath, 2004]. Hence, the plethora of neuroimaging studies in healthy volunteers on the ToL may represent a more homogeneous foundation for examining the functional anatomy of planning processes and for addressing questions concerning the localization and lateralization in the PFC. Most notably in this respect, although planning is commonly associated with the mid-dorsolateral prefrontal cortex (dlPFC) [cf., Unterrainer and Owen, 2006], the surprisingly wide-spread distribution of prefrontal peak voxels derived from 31 neuroimaging studies on the ToL (see Fig. 3) does not imply a clear focus of planning-related neural activation within mid-dlPFC and thus runs counter to this common tenet. The term “dlPFC” is in fact used to refer to an extended prefrontal area that covers parts of the middle and superior frontal gyri and thus includes the functionally different, Brodmann areas (BA) 9, 9/46, 46, and parts of 8 and 10 [Petrides, 2005]. Therefore, the precise spatial localization of

planning processes within the dlPFC is highly relevant for correctly identifying the neural underpinnings of planning processes. That is, adding to the unresolved issue of a possible lateralization of PFC involvement in planning (cf., Table B1) [see also Cazalis et al., 2003; Kaller et al., 2011b], the often assumed association with its mid-dorsolateral part [e.g., Unterrainer and Owen, 2006] remains to be empirically confirmed by a quantitative examination of activation coordinates across studies.

Quantitative meta-analyses have a long history in clinical research [O'Rourke, 2007] but have also become increasingly popular in functional neuroimaging [e.g., Eickhoff et al., 2006; Farrell et al., 2005; Price et al., 2005; Wager et al., 2004; Wager and Smith, 2003], as they allow assessing brain-behavior relationships independent of study-specific confounds such as characteristics of samples and experimental procedures, task implementation, imaging parameters and artefacts, preprocessing, statistical thresholds, and correction mechanisms. As one of the most common algorithms for coordinate-based meta-analyses, activation likelihood estimations (ALE) are computed for the distribution of reported activation peaks of all included studies and compared against random distributions to account for the spatial nature of neuroimaging results [Eickhoff et al., 2009; Laird et al. 2005; Turkeltaub et al., 2012].

In the present study, we therefore adopted this meta-analytic ALE approach with the aim of examining the functional anatomy of planning processes and particularly with the aim of resolving the open questions on the specific localization and the hemispheric lateralization of PFC involvement. To this end, the meta-analysis was based on functional neuroimaging studies using the ToL, as it constitutes the most frequently applied experimental planning paradigm in clinical and cognitive neuroscience [Kaller et al., 2011a].

METHODS

Study Selection

The web-hosted databases *PubMed* (www.ncbi.nlm.nih.gov/pubmed), *ISI Web of Knowledge* (www.webofknowledge.com), *Science Direct* (www.sciencedirect.com) and *PsycINFO* (www.apa.org/psycinfo) were searched using pair-wise combinations of the key term *ToL* with the following terms: *fMRI*, *functional magnetic resonance imaging*, *PET*, *positron*

Box 1. Overview on prefrontal lateralization of planning ability in lesion studies.

In addition to the ALE analyses presented in the main text, we conducted a literature search for studies on the Tower of London task in patients with frontal brain lesions. The aim was to provide another approach particularly on the question of hemispheric lateralization of human planning. To identify studies that compared right against left frontal lesioned patients, all studies from the original literature search were rescanned. Identified studies were checked for cross references of further suited studies. The literature research revealed 13 studies in total that examined the ToL task (cf., Fig. 1) in patients with frontal brain lesions. However, note that not all of these reported patient samples were independent, as some studies reported (partly) overlapping samples (indicated in Table B1) [cf. Owen et al., 1990, and Pantelis et al., 1997]. Furthermore, descriptive statistics or verbatim information on the comparisons of interest here (frontal lesion patients vs. controls, left- vs. right frontal lesion patients) were not at all available for some studies [Cockburn, 1995; Levin et al., 1994; Shallice et al., 1989] whereas many of the remaining studies did not differentiate between left and right frontal lesions [Anderson et al., 2002; Andrés and Van der Linden, 2001; Andrews et al., 2014; Jacobs and Anderson, 2002; Pantelis et al., 1997; Shum et al., 2009].

In consequence, demographic and performance data from 10 studies reporting effects of (pre)frontal lesions on planning ability was extracted (see Table B1 for an overview). To allow for comparison of effect sizes between studies, if descriptive and/or inferential statistics were reported, Hedges' g was calculated [Hedges and Olkin, 1985]. If no statistical characteristics but only verbatim descriptions of observed results were reported in the original studies (e.g., Shallice, 1982: "the left anterior group was the slowest of all", p. 205) effects were listed descriptively (e.g. $le > ri$).

Given the small overall number of studies together with the heterogeneity of reported information, a formal assessment in terms of a meta-analysis was not feasible. A brief overview and summary of the results is therefore listed below.

Frontally Lesioned Patients Compared to Healthy Controls

A total of six studies reported a reduced planning accuracy in patients compared to healthy controls [significant: Andrews et al., 2014, Owen et al., 1990, 1995, Shum et al., 2009; not significant: Jacobs and Anderson, 2002, Pantelis et al., 1997] whereas only one study [Anderson et al., 2002] reported an opposite pattern (significantly higher accuracy in frontally lesioned patients). An increased number of executed moves as another index of impaired planning was observed for frontally lesioned patients in three studies [significant: Carlin et al., 2000, Owen et al., 1990; not significant: Pantelis et al., 1997]. Although not significant, one study [Andrés and Van der Linden, 2001] found effects in the other direction (decreased number of executed moves).

A prolonged initial thinking (or pre-planning) time for lesioned patients was observed in four studies [significant: Pantelis et al., 1997; not significant: Andrés and Van der Linden, 2001, Jacobs and Anderson, 2002, Shum et al., 2009]. One study reported a (not significant) reduction in initial thinking time [Carlin et al., 2000]. For another three studies, no information on the direction of effects on initial thinking time was available [Andrews et al., 2014, Owen et al., 1990, 1995]. The movement execution time of patients was prolonged in four studies [all significant: Andrés and Van der Linden, 2001, Carlin et al., 2000, Owen et al., 1990, Pantelis et al., 1997].

Left Frontally Lesioned Compared to Right Frontally Lesioned Patients

With respect to the hemispheric lateralization of planning in well-structured tower tasks, none of the studies reported any significant findings, but descriptions of the effects' directions. A total of two studies observed a lower accuracy in left lesioned versus right lesioned patients [Carlin et al., 2000, Shallice, 1982] and another two studies [Owen et al., 1990, 1995] reported non-significant results without specifying the direction. The number of executed moves was increased for left lesioned versus right lesioned patients in one study [Carlin et al., 2000], whereas one study reported [Owen et al., 1990] non-significant effects without specifying the direction.

Initial thinking time was increased for left lesioned patients in one study [Shallice, 1982] and for right lesioned patients in one study [Carlin et al., 2000], another two studies [Owen et al., 1990, 1995] reported non-significant effects without specifying the direction. Movement execution time was prolonged for left lesioned patients in one study [Carlin et al., 2000]; again one study [Owen et al., 1990] reported non-significant results without specifying the direction.

Taken together and summarized in Table B2, comparing frontally lesioned patients to healthy controls often results in a reduced planning accuracy and, occasionally, in an increased number of executed moves, while initial thinking time and movement execution time are prolonged in some but not all cases. Neither a clear pattern nor any significant findings emerges for comparing left and right frontally lesioned patients in common performance and latency measures of planning in well-structured tasks. However, when interpreting these results, it has to be borne in mind that the studies mostly consisted of small sample sizes and presumably comprised a heterogeneous collection of etiologies (e.g., stroke, tumor, trauma) with different courses of disease and brain plasticity.

TABLE B1. Overview of studies on the Tower of London task investigating planning ability in frontally lesioned patients

Study	Sample				Task		Respected Effects								
	N		Sex (m/f)	Age M±SD (years)		Tower Type	Minimum Moves	Accuracy		Number of Executed Moves		Initial Thinking Time		Movement Execution Time	
	Pat/NC	le/ri/bi	Pat	NC	Pat			NC	Pat vs. NC	le vs. ri	Pat vs. NC	le vs. ri	Pat vs. NC	le vs. ri	Pat vs. NC
Anderson et al. [2002]	20/80	15/5	43/37	11.4± 2.9	9.4± 2.8	ToL	2-5	0.11							
Andrés and Van der Linden [2001]	13/13	6/4/3	13/0	33.2± 13.8	32.8± 13.2	ToL	3 5 neutral 5 facilitating 5 misleading			-0.35 -0.06 -0.16 -0.42	0.41 0.71 0.56 0.18 n.s.			0.69 1.31** 0.33 0.49	
Andrews et al. [2014]	14/40	7/4/3	7/7	24/16	64.29± 8.82	68.28± 12.16	ToL 4-D	2-9	-1.02**						
Carlin et al. [2000]	14/15	7/5/2	10/4	11/4	59.9± 12.6	57.5± 16.6	ToL	2-5 2-3 4-5		-0.23 -0.39 0.71	0.69* -0.39 0.71	-0.06 -0.21 -0.22 0.14		0.87** -0.26 0.94†	0.14
Jacobs and Anderson [2002]	31/38	12/9/10	19/12	19/19	11.3± 2.8	10.8± 2.7	ToL	2-5	-0.18						
Owen et al. [1990] ^{#1}	26/26	8/15/3	14/12	14/12	43.0± 18.8	44.6± 17.7	ToL (SoC)	2-5	-0.63*	n.s.	.59*	n.s.	n.s.	0.60*	n.s.
Pantelis et al. [1997] ^{#1}	26/31	8/15/3	15/11	18/13	41.73± 19.1	47.48± 11.6	ToL (SoC)	2 3 4 5	0.24 -0.18 -0.17 -0.34		-0.24 0.19 0.12 0.29	0.27 0.58† 0.54† 0.27		0.59† 0.55† 0.59† 0.64†	
Owen et al. [1995]	17/10	5/10/2	9/8	7/10	46.5± 18.1	44.1± 13.3	ToL (SoC)	1-5	-1.28***	n.s.			n.s.		
Shallice [1982]	61/20						ToL	2-5		le < ri			le > ri		
Shum et al. [2009]	15/15						ToL 4-D	2-9 2-5 6-9	-0.82* -0.39 -0.80*			0.04 0.45 -0.05			

^aNote. If descriptive statistics were available, the here reported effect sizes were computed as Hedges' g [Hedges and Olkin, 1985] allowing comparisons across studies. Otherwise effects were reported verbatim (e.g., $le > ri$, n.s.). Significant results are highlighted in bold font (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; n.s., not significant). Stars (*) indicate P -values reported by the authors whereas crosses (†) indicate posterior tests of significance (Students t -test for independent groups and unequal sample sizes) by the authors of the present study based on the available data. Superscripts starting with hashtags followed by numbers indicate partly or fully overlapping samples between the studies. Abbreviations: N, sample size; m, male; f, female; Pat, patients; NC, normal controls; le, left frontal lesion; ri, right frontal lesion; bi, bilateral frontal lesion; ToL, Tower of London; SoC, Stockings of Cambridge; 4-D, four-disc version.

TABLE B2. Overview on the frequency and direction of effects on planning performance across lesion studies

Number of studies overall (number of studies with significant effects or trends)			
Pat vs. NC	Pat < NC	Pat > NC	No direction reported
Accuracy	6 (4)	1 (0)	0
Executed moves	3 (2)	1 (0)	0
ITT	4 (1)	1 (0)	3
MET	4 (4)	0 (0)	0
Left vs. Right	Left < Right	Left > Right	No direction reported
Frontal			
Accuracy	2 (1)	0 (0)	2
Executed moves	1 (0)	0 (0)	1
ITT	1 (0)	1 (1)	2
MET	1 (0)	0 (0)	1

Abbreviations: Pat, patients; NC, normal controls; ITT, initial thinking time; MET, movement execution time.

emission tomography, SPECT, single photon emission computed tomography, NIRS, near infrared spectroscopy, EEG, electroencephalography, planning, problem solving, brain imaging, functional imaging, activity. In addition to these brain-imaging specific search terms, the key term *ToL* was also combined with the broader terms *planning* and *problem solving* to maximize chances for detecting all relevant studies. The present literature search included all studies published until December 2014.

Figure 1.

Illustration of the ToL disc-transfer task. The tower configuration consists of three balls placed on three rods of different heights. The start configuration of the balls has to be transformed into a given goal configuration while considering several rules. The major rules for transformation are identical for the two tasks: Only one ball can be moved at once, a ball must not be placed beside a rod, and only the topmost ball of each rod can be moved. The three balls differ in their color and the rods in their length and capacity for holding balls. The left rod can hold up to three balls, the middle rod up to two balls, and the right rod only one ball. Subjects are commonly instructed to solve a given problem in the minimum number of moves. Planning ahead is hence required for efficient problem solving in terms of attaining the optimal solution.

As illustrated in the flow chart in Figure 2, 636 individual reports were identified. During the subsequent selection process, abstracts and/or manuscripts were screened and 565 studies excluded as not relevant for the topic. Of the remaining 71 functional imaging reports, another 40 studies did not qualify for the present meta-analysis. A flow-chart of the selection process is provided in Figure 2.

The final selection consisted of 31 independent datasets that were published in 31 neuroimaging papers¹ (Table I). All included studies used three-ball versions of the ToL with either three differently sized pegs ($n = 16$) [cf., Shallice, 1982] or three equally sized pegs ($n = 3$) [cf. Ward and Allport, 1997], or the Stockings of Cambridge (SoC) version with differently sized pockets ($n = 10$) [cf. Owen et al., 1990]. Furthermore, studies differed with respect to the response modes (cf., solution execution in Table I): In some studies, subjects were asked to solve the problems by executing the individual moves ($n = 8$), whereas in other studies, subjects only had to indicate the minimum number required for the optimal solution of a given problem without actually executing these moves ($n = 24$).² However, assuming that planning ahead was required for both types of response modes, these were not further differentiated in the subsequent analyses.

Meta-Analyses on Overall Planning and Planning Complexity

In the majority of functional brain imaging studies using the ToL task, planning-related neural activation is identified by either contrasting planning with a baseline condition or by experimentally manipulating planning complexity with factorial or parametric designs [see overview in Kaller et al., 2011b]. In consequence, in the present ALE study separate meta-analyses were conducted for

¹Note in this respect that Elliot et al. [1997] reported a reanalysis of the data of Baker et al. [1996], whereas Owen et al. [1998] reported a reanalysis of the data of Owen et al. [1996]. However, as the analyses on *Overall Planning* in the original studies were extended in both follow-up studies by analyses of *Planning Complexity*, this additional information was included in the present meta-analysis. Schall et al., [2003] and van't Ent et al. [2014] reported two independent samples each. Den Braber et al. [2008] examined twins where one twin suffered obsessive-compulsive symptoms. Only the reported activations of the healthy twins were included in the present ALE analyses. De Ruiter et al. [2009] examined problem gamblers, smokers, and healthy controls. They reported only the activation foci across all groups, as they did not find interactions between groups and experimental conditions. Therefore, the reported foci of the main effect of planning versus baseline were included; however, solely the sample size and description of the healthy controls were used.

²Studies with versus without solution execution (cf., Table 1) sum up to 32, as one study applied both response modes in two different runs [Rowe et al. 2001] (reported coordinates refer to a collapsed analysis across runs).

Figure 2.

Flow chart illustrating the step-wise study selection procedure.

Overall Planning (compared with a baseline) and for *Planning Complexity*.

The meta-analysis on *Overall Planning* comprised independent 29 datasets with the following control conditions (see Table I): counting balls on screens ($n = 12$); zero-move problems with identical start and goal states ($n = 5$; including one study in which additionally appearing yellow rings had to be touched); ball detection and selection of a blinking ball while constantly tapping the screen ($n = 1$); one-move problems ($n = 2$); problem displayed but subjects were requested not to solve it ($n = 1$); examiner showed the solution and participants had to simply copy moves ($n = 2$; including one study where in an additional control condition empty SoC pockets were presented); counting vowels of words written on the ToL balls ($n = 1$); scrambled, unrecognizable picture of the ToL ($n = 1$); an empty screen or a fixation cross ($n = 4$).

For the meta-analysis on *Planning Complexity*, independent 14 datasets were identified (see Table I). In 10 of these, problem difficulty was modeled as a parametric modulation in terms of the minimum number of moves to solution. In the remaining four datasets, ToL problems were divided into easy versus difficult problems so as to run comparisons for these two types of problems.

ALE Approach

ALE is a method to perform quantitative meta-analysis on functional brain imaging results based on all local activation maxima (resp. foci) [Eickhoff et al., 2009]. The algorithm treats the local maxima not as individual points in space but as spatial probability distributions, so that an activation probability can be computed for every voxel. To

create a null distribution for statistical evaluations, random foci maps are generated based on the same amount of foci as inserted into the meta-analysis. Subsequently, the probability map resulting from the meta-analysis is compared with the random map so as to calculate q values of the false discovery rate (FDR) [Eickhoff et al., 2009].

Present analyses were performed with GingerALE 2.3.2 (www.brainmap.org) using the approach of Turkeltaub et al. [2012] to minimize within-experiment and within-group effects on the overall estimation. Coordinate-based ALE meta-analyses were conducted in Montreal Neurological Institute (MNI) stereotactic standard space. Coordinates of brain activation foci reported in Talairach standard space [Talairach and Tournoux, 1988] were converted into MNI space using the *icbm2tal_spm* algorithm [Lancaster et al., 2007] implemented in GingerALE 2.3.2. All activation foci reported in the included studies were double-checked for plausibility and congruence with the provided anatomical labels. Observed divergences between signs of x -coordinates and reported hemisphere were corrected by reversing the sign before entering the coordinates in the ALE meta-analyses. This correction concerned 13 foci from three studies.³

GingerALE automatically determines full-width-at-half-maximum (FWHM) values, so that no additional FWHM filter was applied here, which conforms to the suggested default analysis procedure (www.brainmap.org). For masking outliers, the *less conservative* approach implemented in GingerALE 2.3.2 was selected. ALE analyses

³The x -coordinates of 10 activation foci from Lazerou et al. [2000], one activation focus from Cohen et al. [2014], and two foci from Schoepf et al. [2011] were accordingly corrected.

TABLE I. Overview of the functional neuroimaging datasets included in the ALE meta-analyses

Data set #	Study	Sample			Task			Number of Reported Activation Foci			
		Imaging technique	N	Sex (m/f)	Mean age (years)	ToL version	Minimum number of moves ^a	Solution execution	Design	Overall planning	Planning complexity
1.1	Baker et al. [1996]	PET	6	5/1	31	SoC	1–6 moves	no	B	20	
1.2	Elliott et al. [1997]	PET	6	5/1	31	SoC	2–3 vs. 4–5 moves	no	B		8
2	Beauchamp et al. [2003]	PET	12	6/6	56.8	SoC	3–5 moves	yes	B	11	
3	Boghi et al. [2006]	fMRI	18	9/9	35.9	WATT	1–3 vs. 4–6 moves	no	n.r.	14	8
4	Campbell et al. [2009]	fMRI	1	1/0	21	Original ToL	n.r.	yes	n.r.	18	
5	Cohen et al. [2015]	fMRI	17	15/2	20.9	WATT	1–7 moves	no	E		13
6	Dagher et al. [1999]	PET	6	2/4	58.6	SoC	1–5 moves	yes	B	29	22
7	de Ruiter et al. [2009]	fMRI	19	19/0	34.1	Original ToL	1–5 moves	no	E	9	9
8	de Ruiter et al. [2011]	fMRI	15	0/15	58.2	Original ToL	1–5 moves	no	E	17	
9	den Braber et al. [2008]	fMRI	12	5/7	32.8	Original ToL	1–5 moves	no	E	13	11
10	Desco et al. [2011]	fMRI	14	9/5	13.4	SoC	2–5 moves	no	B	21	
11	Fallon et al. [2013]	fMRI	52	23/29	64.3	SoC	2–4 moves	no	E	7	
12	Goethals et al. [2004]	SPECT	10	6/4	24	Original ToL	2–6 moves	yes	B	1	
13	Huyser et al. [2010]	fMRI	25	9/16	13.7	Original ToL	1–5 moves	no	E	14	10
14	Just et al. [2007]	fMRI	18	15/3	24.5	SoC	1–3 moves	no	B	13	
15	Kempton et al. [2011]	fMRI	10	5/5	16.8	SoC	2–4 moves	no	E	8	
16	Lazeron et al. [2000]	fMRI	9	5/4	22	Original ToL	2–7 moves	no	B	10	
17	Lazeron et al. [2004]	fMRI	18	12/4	36.6	Original ToL	2–4, 6–8 moves	no	B	8	
18	Liemburg et al. [2015]	fMRI	20	14/6	31.1	Original ToL	1–2 vs. 3–5 moves	no	B	6	3
19.1	Owen et al. [1996]	PET	12	6/6	41.4	SoC	3–5 moves	yes	B	26	
19.2	Owen et al. [1998]	PET	6	4/2	57.7	SoC	3 vs. 4–5 moves	yes	B		1
20	Rasmussen et al. [2006]	fMRI	8	8/0	25	Original ToL	3–5 moves	yes	B	25	9
21	Rowe et al. [2001]	PET	10	10/0	27	SoC	0–9 moves	yes, no	B	17	
22.1	Schall et al. [2003]	PET	6	5/1	33.8	WATT	1–7 moves	no	B		6
22.2		fMRI	6	5/1	31	WATT	1–7 moves	no	B	8	3
23	Schöepf et al. [2011]	fMRI	28	12/16	27.3	Original ToL	n.r.	no	B	9	
24	Spreng et al. [2010]	fMRI	20	3/17	21.3	Original ToL	3–7 moves	no	E	20	
25	Stokes et al. [2011]	fMRI	47	19/28	35.7	SoC	3–5 moves	no	B	8	
26	van den Heuvel et al. [2003]	fMRI	22	11/11	29.9	Original ToL	1–5 moves	no	E	18	26
27	van den Heuvel et al. [2013]	fMRI	11	4/7	25.5	Original ToL	1–5 moves	no	E	20	25
28.1	van't Ent et al. [2014]	fMRI	46	13/33	36.9	Original ToL	1–5 moves	no	E	8	
28.2		fMRI	45	13/32	36.9	Original ToL	1–5 moves	no	E	3	
29	Wagner et al. [2006]	fMRI	17	9/8	27.5	Original ToL	2–5 moves	no	E	10	

Note. Listed are reference numbers and respective studies with author and year of all 31 studies that were included in the ALE analysis on *Overall Planning* or *Planning Complexity*. Moreover, the respective imaging technique, the sample size (overall and separated for gender), mean age of the sample, and the amount of reported activation foci are listed. SoC, Stocking of Cambridge. WATT, Ward and Allport Tower Task.

^aThe minimum number of moves states the all problem difficulties that were utilized in the studies. Moreover, if there is solely a range listed (e.g., 1–5 moves) the reported planning complexity analysis was parametrical whereas if there are two numbers or ranges listed separated by a “vs.” (e.g., 1–3 vs. 4–6 moves) the reported planning complexity analyses was categorical. n.r., not reported; B, block design; E, event-related design.

A. Overall Planning

B. Planning Complexity

Figure 3.

Spatial distributions of activation foci from ToL neuroimaging studies included in the present ALE meta-analyses on (A) *Overall Planning* and (B) *Planning Complexity* (see Methods section for further details). Individual foci are marked by spheres. The sizes and the colors of the spheres refer to the underlying sample

sizes and the used brain imaging techniques. The renderings for the lateral views only comprise the activation foci for the respective hemisphere, whereas the topview renderings represent all foci.

were computed with a FDR of $P < 0.01$ as cluster-forming threshold and $P < 0.05$ for cluster-level inference as recommended in the manual.

RESULTS

The Functional Anatomy of Planning Processes

Meta-analysis of neural activation patterns for overall planning

Of the 31 published neuroimaging papers on the ToL suitable for ALE meta-analysis, 29 independent datasets from 28 studies were included in the analysis on *Overall Planning*, comprising 537 normal subjects (48.8% male) with a mean age ($\pm$ standard deviation, SD) of 32.4 ± 13.1 years. Adjusted for sample size, the weighted mean age was 35.0 years. The analysis was based on a total of 391

activation foci (Fig. 3A), while another 20 foci (5.1%) were disregarded due to a location outside of the applied ALE brain mask (see above).

As illustrated in Figure 4A, results of the ALE meta-analysis on *Overall Planning* activation with a cluster level threshold of $P = 0.05$ and a FDR-threshold of $q < 0.01$ revealed bilateral contributions of mid-dlPFC, which were however more pronounced for its right ([41 36 30], 3,776 mm³) than for its left homolog ([−41 32 31], 2,736 mm³). Results further yielded bilateral involvement of the frontal eye fields (FEFs), caudate, anterior insula, inferior parietal lobule (IPL), supplementary motor area (SMA), precuneus, and rostralateral prefrontal cortex (rlPFC). Lateralized activation was found for right inferior occipital gyrus, right inferior temporal gyrus, and left posterior cingulate. A detailed overview on the contributions of the individual studies underlying these results is provided in Table II.

A. Overall Planning

B. Planning Complexity

Figure 4.

Spatial distribution of resulting activation patterns for the ALE meta-analyses on **(A) Overall Planning** and **(B) Planning Complexity**. White contours reflect the applied FDR threshold of $P < 0.01$. Numbers besides the axial slices refer to z-coordinates in MNI-space.

Meta-analysis of neural activation patterns for planning complexity

The ALE meta-analysis on *Planning Complexity* was conducted on 14 datasets of 13 studies that comprised 182

normal subjects (63.2% male) with a mean age ($\pm$ SD) of 32.9 ± 12.2 years and a weighted mean age of 29.8 years. The analysis was based on a total of 154 activation foci (Fig. 3B), while another seven foci (4.5%) were disregarded

TABLE II. Overview of significant ALE clusters for overall planning and planning complexity

ALE meta-analysis area		Lateralization	Cluster extent (mm ³)	Weighted centroid			Number of foci	Dataset (Reference #)
				<i>x</i>	<i>y</i>	<i>z</i>		
Overall Planning	dlPFC	Left	2736	-40.6	31.8	30.6	10	1.1, 2, 7, 9, 13, 14, 19.1, 20, 24, 27
		Right	3776	41.4	35.5	29.9	13	1.1, 7, 8, 9, 13, 17, 20, 23, 24, 26, 27
	FEF	Left	7552	-26.2	8.7	57.1	26	1.1, 2, 3, 6, 8, 9, 10, 13, 14, 15, 16, 17, 20, 21, 22.1, 24, 25, 26, 27, 28.1, 29
		Right	7160	29.3	11.3	55.2	21	1.1, 3, 6, 8, 9, 10, 11, 13, 14, 15, 19.1, 20, 21, 23, 24, 25, 26, 28.1, 29
	SMA/pre-SMA	Bilateral	3984	-1.9	25.8	43.9	13	1.1, 3, 7, 8, 10, 13, 14, 19.1, 20, 24, 25, 26, 29
	IPL	Left	2200	-38.2	-45.6	44.9	7	2, 7, 10, 15, 19.1, 20
		Right	4376	46.3	-39.8	47.2	15	3, 4, 6, 7, 8, 13, 15, 18, 19.1, 20, 24, 26, 27, 29
	Precuneus	Bilateral	13664	0.0	-61.5	57.3	43	1.1, 2, 6, 7, 8, 9, 10, 11, 13, 14, 15, 17, 18, 1.9, 20, 21, 23, 25, 26, 27, 28.1, 28.1, 29
		Right	1512	32.9	-72.1	42.5	8	1.1, 6, 9, 19.1, 21, 26
	Caudate	Left	1776	-12.2	14.3	1.0	7	4, 7, 9, 13, 26, 27, 28.1
		Right	1232	13.9	10.1	2.6	5	2, 7, 9, 26, 27
	Anterior insula	Left	2000	-31.0	23.8	-0.9	7	6, 13, 14, 20, 24, 25, 27
		Right	2784	33.1	24.3	-4.2	10	1.1, 13, 14, 20, 21, 24, 25, 26, 27, 29
	rlPFC	Left	2600	-35.3	55.8	5.6	9	8, 9, 13, 14, 20, 25, 28.1, 28.1, 29
		Right	648	33.7	57.6	3.8	4	9, 11, 23, 25
	Posterior cingulate	Left	792	-17.1	-58.2	21.5	3	8, 11, 28.1
	Inferior Occipital Gyrus	Right	656	43.3	-79.2	-4.1	3	19.1, 24
	Inferior Temporal Gyrus	Right	624	52.1	-62.1	-5.7	2	8, 23
Planning Complexity	dlPFC	Left	2832	-43.2	32.8	30.9	8	6, 7, 9, 1.2, 20, 26, 27
		Right	1808	42.2	38.7	27.3	6	5, 6, 7, 9, 26
	FEF	Left	512	46.0	26.1	42.8	2	18, 27
		Left	1728	-24.8	-0.9	65.2	5	9, 13, 26, 27
		Right	1176	-25.0	22.5	53.3	5	3, 6, 18, 26
		Right	1576	29.6	17.5	55.9	5	3, 5, 6, 26, 27
		Left	400	22.8	-5	66.0	2	9, 13
		Bilateral	2504	-3.5	24.5	45.6	7	3, 5, 7, 13, 22.1, 26, 27
	IPL	Left	808	-53.8	-40.7	48.8	3	7, 26, 27
		Right	728	-40.5	-51.9	51.0	3	5, 9, 27
		Right	1792	51.2	-42.8	46.7	7	3, 7, 9, 20, 26, 27
		Left	1832	-11.1	-57.7	60.9	4	5, 7, 13, 26
	Precuneus	Right	1848	8.3	-59.3	58.4	5	7, 13, 26, 27
		Right	504	42.4	-74.8	39.3	2	13, 26
	Caudate	Left	2432	-16.4	7.5	11.1	8	6, 7, 9, 13, 27
		Right	1184	18.3	6.8	15.6	3	7, 13, 26
		Left	520	14.1	5.2	-2.1	2	26, 27
		Left	504	-32.9	23.1	-4.5	2	26, 27
	Anterior insula	Left	504	-32.9	23.1	-4.5	2	26, 27
	rlPFC	Left	1176	-40.0	55.5	10.4	5	9, 1.2, 26, 27

Note. Results are reported at a threshold of FDR $P < 0.01$ and a cluster extent of 50 mm³. The *number of foci* contains the number of individual activation foci that contributed to the respective cluster. *Dataset (Reference #)* refers to the respective column in Table I. Differences between the *number of foci* and the number of listed *datasets* are due to multiple foci of single studies within the same brain area. dlPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; SMA, supplementary motor area; IPL, inferior parietal lobule; rlPFC, rostralateral prefrontal cortex.

Figure 5.

(A) BA 46 distribution maps in five human post-mortem brain dissections (left) and their resulting overlay in the Talairach and Tournoux [1988] space. Reproduced and adapted from Rajkowska and Goldman-Rakic, *Cereb Cortex*, 1995b, 5, 323–337, reproduced by permission (B + C) Overlay of BA 46 as

described by Rajkowska and Goldman-Rakic [1995a,b] (gray) and the activation cluster in midPFC (red) resulting from the ALE meta-analyses for (B) *Overall Planning* and (C) *Planning Complexity* (rendered at a FDR-correction of $P < 0.01$). IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus.

given a location outside the applied ALE brain mask (see above). Results for the cluster level threshold of $P = 0.05$ and the FDR-threshold with $q < 0.01$ yielded a bilateral lateralization for mid-dIPFC with a more pronounced activation extent in left ($[-43\ 33\ 31]$, $2,832\ \text{mm}^3$) compared to right mid-dIPFC ($[42\ 39\ 27]$, $1,808\ \text{mm}^3$) (Fig. 4B). In addition, bilateral involvement was found for the FEFs, precuneus, SMA, IPL, and caudate as well as a left lateralization for the rIPFC and anterior insula. Detailed results as well as the individual contributing studies are listed in Table II.

The Anatomical Localization of Planning Processes in the dIPFC

The localization of planning processes within left and right dIPFC and, in particular, the empirical validation of their putative assignment to the mid-dIPFC [Unterrainer and Owen, 2006] as a circumscribed cytoarchitectural structure in terms of BA 46 (and 9/46) [cf., Rajkowska and Goldman-Rakic, 1995a,b] were main objectives of the present meta-analysis. However, as of yet, probabilistic maps for BA 46 are not available at the voxel level of a stereotactic standard space. We therefore projected the spatial distribution of BA 46 estimated from the five post-mortem brains investigated by Rajkowska and Goldman-Rakic [1995b] onto the renderings of the mid-dIPFC activation for *Planning Overall* and *Planning Complexity* (Fig. 5). The resulting overlap indicates that planning is indeed specifically associated with activation of a spatially circumscribed part in the center of the middle frontal gyrus presumably corresponding to BA 46. Furthermore, the overlay with the cytoarchitectural projections of BA 46 suggests that the activation in mid-dIPFC for overall planning and particularly for planning complexity slightly

extends in the caudal direction presumably corresponding to BA 9/46 [cf., Petrides, 2005; Petrides and Pandya, 1999].

The Hemispheric Lateralization of Planning Processes in the PFC and beyond

ALE contrast analysis

The above reported lateralization of mid-dIPFC activation during planning was so far assessed only at a descriptive level and revealed larger activation extents for left and right mid-dIPFC for analyses of *Overall Planning* and *Planning Complexity*, respectively (see The Functional Anatomy of Planning Processes section and The Anatomical Localization of Planning Processes in the dIPFC section).

To statistically contrast left and right mid-dIPFC activations at the voxel level, we further transformed the respective foci into a common space. To this end, we used the mid-dIPFC activations centers (or weighted centroids) derived from the Overall Planning meta-analysis. To determine the activation extents, inspection of the distance histograms showed that activation foci from individual studies clustered within a range of 20 mm from the weighted centroids. In consequence, all activation foci within this distance were included in the ALE contrast analysis and transformed into a common space by subtracting the weighted centroids. In total, 13 coordinates from the left and 15 from the right hemisphere were included.

Performing an ALE contrast meta-analysis revealed no lateralization effects for left versus right mid-dIPFC on the voxel level. A control analysis in which the coordinates from the right hemisphere were mirrored (in x -direction) with respect to the right centroid (so as to account for the brain surface's convexity) did also not yield any

lateralization effects. Note however that both analyses were highly unlikely to have sufficient statistical power to detect (subtle) differences given the relatively small number of analyzable studies and activation foci.

Exploration of systematic differences between studies

To assess whether systematic methodological differences may account for lateralization differences between studies, all studies included in the ALE meta-analyses for *Overall Planning*⁴ were divided into four groups according to the presence of planning-related activations in left mid-dIPFC (yes/no) and right mid-dIPFC (yes/no) thus resulting in a 2×2 contingency table (cf., Table II). This yielded 16 studies without any activation peaks in the mid-dIPFC, another three studies with exclusively left and three studies with exclusively right mid-dIPFC activation peaks, and seven studies with bilateral mid-dIPFC activation peaks. Analyses of potential between-study differences concerned the subjects' age and sex ratio and the average and maximum of the applied problem's minimum moves which were entered as dependent variables in separate ANOVAs with subdivisions of studies according to left and right dIPFC activation patterns as between-study factor. However, no significant between-study differences could be observed for any of these variables (for detailed results, see Supporting Information Table S1). But given that two of the four groups only comprised three studies the negative findings may be due to insufficient power.

Further explorative analyses concerned study characteristics such as study design (block vs. event-related), imaging technique (fMRI vs. PET), modeling approach (categorical vs. parametric), solution execution (moves executed vs. moves not executed), and ToL version (original ToL version vs. SOC) which were nominally coded and hence entered together with the 2×2 study subdivision (see above) into analyses of multi-dimensional contingency tables. Notably, these analyses suffered heavily from zero-frequency cells and most cells with a frequency lower than five which may result in severe distortions. However, the analyses appear to indicate some important differences: In studies applying the original ToL version, the occurrence of right dIPFC activation was balanced (irrespective of left dIPFC activation), whereas none of the studies applying the SOC found activation in right dIPFC (see Supporting Information Table S2). Moreover, the study design (block vs. event-related) also appeared to affect the probability of right-lateralized activation (see Supporting Information Table S4). In studies with event-related designs activation of right dIPFC was slightly more frequent, whereas in studies with block designs the number of studies *without* reporting activation of right dIPFC was four times higher than that of studies reporting activation in right dIPFC.

⁴Note that between-study analyses on *Planning Complexity* were not carried out due to the limited number of data sets.

However, these effects of ToL version and study design were not independent ($\chi^2_1 = 5.882$, $P = 0.015$, see also Supporting Information Table S8), as studies applying the SOC more often used block design and studies applying the original ToL more often used event-related designs. Neither the comparison of imaging techniques nor modeling approach nor solution execution yielded any significant differences (see Supporting Information Tables S2).

Whole-brain lateralization analyses

To examine lateralization effects beyond the (mid-)dIPFC, two additional whole-brain ALE contrast analyses were performed separately across all foci from *Overall Planning* and from *Planning Complexity*. For *Overall Planning*, two areas were found to have stronger activation on the right hemisphere than on the left hemisphere, namely the IPL and premotor cortex (see Supporting Information S2 for detailed results). For *Planning Complexity*, a stronger activation was observed in the left compared to the right SMA.

DISCUSSION

The present ALE meta-analyses on 29 neuroimaging datasets using the ToL task yielded two major findings on the specific involvement of the dIPFC in human planning. First of all, the results corroborated that planning-related activation in dIPFC is localized in circumscribed neural assemblies in the mid-dorsolateral part of the PFC [cf., Unterrainer and Owen, 2006], presumably corresponding to BA 46 [Petrides, 2005; Petrides and Pandya, 1999; Rajkowska and Goldman-Rakic, 1995a,b] and possibly to caudally adjacent parts of BA 9/46 [Petrides, 2005; Petrides and Pandya, 1999]. Second, results clearly emphasized the importance of bilateral mid-dIPFC for planning in tasks like the ToL.

The Localization of Planning Processes within the Mid-dIPFC

The present study revealed the involvement of the bilateral dIPFC in well-structured planning. Moreover, instead of the extended area of the dIPFC that is referred to in most ToL studies, mainly comprising BA 9, 9/46, and 46 [cf., Petrides, 2005, 2013; Petrides and Pandya, 1999], but sometimes also parts of BA 6, 8, and 10, the middle part of the dIPFC (mid-dIPFC) emerged as the essential sub-region for planning in the present meta-analysis. Importantly, the present meta-analyses particularly emphasize the functional distinction between BA 9 and BA 46 (see Fig. 5) in that overlapping the present results with the human cytoarchitectonic maps from Rajkowska and Goldman-Rakic [1995b] suggests planning-related brain activity in mid-dIPFC to be confined to BA 46 (Fig. 5) and, if following the nomenclature by Petrides [2005, 2013], extending slightly into caudally adjacent parts of BA 9/46.

Cytoarchitecturally, the mid-dlPFC is a brain area with a relatively large layer thickness and, on average, with a high neuronal packing density [Rajkowska and Goldman-Rakic, 1995a]. The layers of BA 46 and BA9/46 are characterized by a well-developed internal granular layer (IV) [Fuster, 2015; Petrides, 2005, Petrides et al., 2012] and, for BA 46, an external pyramidal layer (III) with only small to medium pyramidal neurons [Petrides, 2005; Petrides and Pandya, 1994, 1999; Petrides et al., 2012]. By contrast, BA 9 has a poorly developed layer IV with lower neuronal density than BA 46 and 9/46 and comprises large pyramidal neurons in layer III [Petrides, 2005; Petrides et al., 2012; Petrides and Pandya, 1999]. In terms of connectivity based on tracer studies in monkeys [e.g., Petrides and Pandya, 1999, 2002; Schmahmann and Pandya, 2006; for a review, see Yeterian et al., 2012], the three areas share a common basic pattern in that they are connected with each other and with other prefrontal and frontal areas (mainly BA 6, 8, 10, 45, and 47), multimodal temporal areas, the anterior and posterior cingulate, and receive afferents from the retrosplenial cortex. Critically although, BA 46 and 9/46, but not BA 9, are reciprocally connected to medial as well as inferior and superior lateral parietal areas and send efferents to the retrosplenial cortex [Petrides, 2005; Petrides et al., 2012; Petrides and Pandya, 1999, 2006]. Thus, BA46 and 9/46 are distinguishable from BA 9 by their strong connection to heteromodal parietal areas that were also found here to form part of the planning network (cf. Fig. 4, Table II), such as the IPL and precuneus (see below), as well as a reciprocal connection to the retrosplenial cortex. Given that Brodmann's [1908] and Walker's [1940] descriptions of area 46 in humans and macaque monkeys, respectively, suggest a very similar cytoarchitecture [Petrides, 2005], it is likely that not only the functional properties of BA 46 and BA 9/46 but also their structural connections share a substantial amount of commonalities in both species and give hence rise to comparable cognitive functions [cf., Petrides, 2005, Petrides and Pandya, 1999]. Thus, considering this connectivity pattern, it has been argued that BA 6 and 8 subserve the simple maintenance of visuo-spatial working memory contents, whereas the higher-order monitoring and manipulation of these representations is subserved by BA 46 and 9/46, that is, the mid-dorsolateral PFC [Petrides and Pandya, 1994, 1999; Petrides 2005].

In sum, when considering the cytoarchitecture and anatomical connections of the dlPFC, current results can be regarded as reflecting bilateral activity of the mid-dlPFC, specifically located in BA 46, during human planning, which in turn represents a prototypical example of goal-directed higher-order cognitive processes in the visuo-spatial domain.

The Role of the Left and Right Mid-dlPFC in Planning

The present meta-analysis demonstrated the involvement of the bilateral mid-dlPFC in planning, which runs

contrary to the tenet of a strictly lateralized involvement of either left or right mid-dlPFC. Furthermore, a relative lateralization suggesting a stronger activation of left over right mid-dlPFC or vice versa could not be found (see The Hemispheric Lateralization of Planning Processes in the PFC and beyond section) but has to be interpreted with caution given the small number of studies underlying this comparison.

Furthermore, as not all studies included in the meta-analysis have uniformly reported bilateral dlPFC activation, the question remains whether methodological differences between the studies may have driven the differences concerning unilateral and bilateral dlPFC involvement during planning. Explorative analyses indicated two (partially confounded) between-study differences entailing stronger contributions of left compared to right dlPFC, namely the tower version (SoC vs. original ToL) and the task design (block vs. event-related presentation and modeling of hemodynamic responses). It could hence be that block designs are generally less effective to detect right dlPFC activation during planning. This interpretation is supported by recent comparisons between stimulus-locked and response-locked modeling approaches for fMRI data on the ToL showing that activation in left mid-dlPFC was elicited particularly early during the planning phase and for a longer period of time, whereas activation in right mid-dlPFC occurred later in the planning phase and for a shorter period of time [Ruh et al., 2012] (see also below). Activation of right mid-dlPFC during planning seems hence more likely to be attenuated by coarse block-type modeling of the hemodynamic response across several problem items. In this regard, one might further question whether the common modeling approach—be it event- or block-related—of convolving a canonical hemodynamic response function across the duration of one or several problem items is appropriate at all for fitting hemodynamic changes during complex cognitive task such as planning. That is, this approach goes along with the implicit assumption of a continuous neural activation during the totally modeled complete course of cognitive processing, which may not equally hold for all brain areas involved and all cognitive processes modeled. That is, modeling approaches using sets of finite impulse response basis functions, which allow for a closer and area-specific fit to the actual course of the hemodynamic response during longer intervals of cognitive processing, may constitute a promising modeling alternative in future studies [e.g., Kaller et al., 2011a,b, Ruh et al., 2012].

As an alternative interpretation, the effects of tower version (which were however associated with the aforementioned effects of task design), may further indicate structural differences between the ToL versions and/or the applied problem sets [e.g., Kaller et al., 2011a,b and Newman et al., 2009] (see also below for effects of problem structure on neural activation patterns). In this regard, the SoC versions compared to the original ToL versions may

have used problems that tap differently into specific planning processes that are performed by the left and right dlPFC. However, these potential explanations warrant caution, as the two effects of between-study differences on dlPFC lateralization during planning were not independent and cannot be unambiguously interpreted.

Taken together, present results clearly demonstrate that the left and right mid-dlPFC are jointly activated both during planning in general and as a function of the complexity of the ToL problems to be solved in particular. However, the finding of a bilateral activation does not preclude that the left and right mid-dlPFC subserve differential roles during the overall planning process. This raises the question as to what these supposed differential roles might be.

Newman et al. [Newman et al., 2003, 2009; Newman and Pittman, 2007] systematically manipulated structural problem parameters of the ToL. They concluded that the left mid-dlPFC is responsible for control processes as well as the representation and maintenance of general task demands, whereas the right mid-dlPFC is associated with integration, manipulation, and maintenance of information in working memory that serve to formulate a strategy for solving a given problem [Newman et al., 2009; cf. Newman and Pittman, 2007].

Kaller et al. [2011b] examined the functional lateralization of the mid-dlPFC using a comparable approach of manipulating structural problem parameters of the ToL. Foundation of the experiment was the concept that the overall planning process dissociates into two separable phases, an early internalization phase (transfer of the start and goal into working memory) and the subsequent core planning phase, where the start is mentally manipulated until its representation matches the goal [cf., Newell and Simon, 1972]. It was found that the internalization phase elicited stronger activation of the left mid-dlPFC, whereas the core planning phase elicited stronger activation in the right mid-dlPFC [Kaller et al., 2011b]. Moreover, the data revealed that the left mid-dlPFC activated earlier during the time course of each trial and that internalization processes occurred only initially [Ruh et al., 2012]. In contrast, the right mid-dlPFC activated especially during the end of the planning phase and the core planning process was found solely here [Ruh et al., 2012].

In a similar focus on the time course of cognitive sub-processes during planning, Byrd et al. [2011] examined the temporal course of the planning phase which was separated into three parts. In the first part bottom-up stimuli processing was observed [Byrd et al., 2011]. In the second part, the stimuli were being processed by the (right) dlPFC. During the last part of the planning phase, again a left dlPFC activation was reported.

In interpreting the present findings, it has to be noted that the mid-dlPFC is found to be involved in a great variety of tasks as a part of the multiple demand (MD) network [Duncan, 2010; Duncan and Owen, 2000]. That is,

the very specificity of planning processes that is ascribed to the left and right dlPFC fades in view of their general involvement in complex cognitive tasks. Yet, this study aimed at delineating the neural basis of planning by conducting a meta-analysis on functional imaging studies using the ToL. Thus, a characterization of the role of the mid-dlPFC in planning was the focus of this work, not a characterization of the range of cognitive processes requiring (mid-)dlPFC involvement. Notwithstanding this, a complete understanding of dlPFC functioning would greatly benefit from future meta-analyses complementing the present one that explicitly investigate the range of cognitive processes drawing on the (mid-)dlPFC. In this regard, a characterization of the precise cognitive and neural processes underlying human planning could then be conceptualized as specific examples of more general, domain-independent cognitive processes subserved by the dlPFC in giving rise to higher-order human cognition.

It has also to be noted that well-structured tasks like the ToL exert different demands on planning ahead than problems in real-life situations [e.g., Burgess, 2000; Goel, 2010]. Hence, the here established significance of bilateral mid-dlPFC for planning in the ToL does not necessarily extrapolate to planning ahead solutions to real-world problems.

Finally, the preceding sections emphasized the crucial role of the mid-dlPFC for planning. However, not all included studies found activation that contributed to the mid-dlPFC clusters, which seems to argue against this critical role of the mid-dlPFC. Possible reasons for this discrepancy are discussed in the following. In the present meta-analysis, the clusters with the largest effect sizes and the highest number of contributing activation foci (cf., Table II) were found in the FEFs (and the precuneus). For ALE analyses, the peak voxel of a given significant cluster is taken as representation of the underlying activation pattern. However, if activations of multiple functionally distinct regions form one large cluster, then the peak of activation does not necessarily constitute an adequate representation of all areas within that large cluster. Given that the FEFs and the dlPFC are located relatively close to each other, the dlPFC-although significantly activated at the voxel level-might not have contributed an activation focus to the meta-analysis, as the activation peak of its cluster lay in the FEFs. Indeed, connected activation clusters of the FEFs and dlPFC can be found in some of the studies that did not contribute a dlPFC activation focus [e.g., Campbell et al., 2009; Dagher et al., 1999; van't Ent et al., 2014]. Another reason might be the issue of varying significance thresholds, which are chosen rather arbitrarily and differ between studies [Lieberman and Cunningham, 2009]. To be specific, in several of the studies not contributing to the dlPFC activation of the ALE analyses, dlPFC clusters are nonetheless visible (in illustrations at liberal thresholds) that, however, do not pass the given significance threshold of that particular study [e.g., Boghi et al., 2006; Desco et al., 2011; Lazeron et al., 2000; Liemburg

et al., 2015; Rowe et al., 2001; Schall et al., 2003; Wagner et al., 2006]. To appropriately address this widely recognized issue of threshold effects, it was recently suggested that in imaging studies all activation independent of significance should be depicted [Allen et al., 2012]. In sum, owing to these methodological considerations, the fact that not all studies included in the meta-analyses contributed foci of dlPFC activation (i) does not necessarily imply that the dlPFC was not involved during planning in these studies at all and (ii) does not generally argue against the pivotal role of the dlPFC for planning ability.

The Functional Anatomy of Planning Processes beyond (Mid)-DLPFC

Concurring with the known anatomy and connectivity of BA46 and BA 9/46, the present ALE meta-analyses revealed a planning-related network of brain regions comprising prefrontal, premotor, parietal, and insular regions as well as the caudate nucleus. In terms of functional networks, these areas substantially overlap with recent conceptions of fronto-parietal networks that underlie the executive control of complex behavior. For instance, the dlPFC and rPFC, IPL, the anterior insula, and the caudate nucleus can be assigned to a circumscribed fronto-parietal control network which is engaged in a variety of tasks that demand controlled information processing [Vincent et al., 2008]. In line with the network's role in planning performance, these tasks can be summarized as taxing higher-order, adaptive top-down control functions [Dosenbach et al., 2007, 2008; Fair et al., 2007]. Moreover, large parts of these fronto-parietal networks can also be ascribed to the MD network [Duncan, 2010; Duncan and Owen, 2000], namely the inferior frontal sulcus, anterior insula, the pre-SMA, and rostral PFC. The MD network is observed in a great variety of functional imaging studies and is characterized by its involvement in fluid intelligence and other complex, goal-directed activities [see Duncan, 2013, for dedicated review].

Remaining areas of the present analysis, namely the FEFs, posterior parietal cortex, intraparietal sulcus, superior parietal lobule and also the pre-SMA emerge as main parts of the dorsal attention network [Vincent et al., 2008] which is assumed to be involved in spatial attention, eye movements, and hand-eye coordination and, hence, concurs well with the attentional as well as visuo-spatial processes induced by performing the ToL.

There have also been attempts to ascribe specific function to the single areas rather than consider them a network. Cognitive processing within rIPFC is assumed to operate on a higher-order level in that the rIPFC is responsible not for devising or executing moves of the ToL, but rather for selecting, evaluating, and monitoring sequences of moves [Baker et al., 1996; Boghi, et al., 2006; Elliot et al., 1997; Rasmussen et al., 2006; Schöpf et al., 2011; cf. Van den Heuvel et al., 2003; Wagner et al., 2006]. The FEFs are

also located in the frontal lobe and are thought to control eye-movements and attention [Baker et al., 1996; Boghi, et al., 2006; Dagher et al., 1999; den Braber et al., 2008; Desco et al., 2011]. The pre-SMA is assumed to also manage attention during planning [Baker et al., 1996; Boghi, et al., 2006].

The present analysis further confirmed the contribution of parietal areas. The superior parietal lobule and the precuneus are relatively uniformly associated with visuo-spatial processing and attentional representation, that is, with the visuo-spatial working memory component of planning [Baker et al., 1996; Beauchamp et al., 2003; Boghi et al., 2006; de Ruiter et al., 2011; den Braber et al., 2008; Desco et al., 2011; Rasmussen et al., 2006; Wagner et al., 2006].

The insula and the nucleus caudate are both mostly neglected in considerations of individual area. For the insula, the automatic sequencing of moves [Baker et al., 1996] but also the salience processing and shifting between the default mode and the dorsal attention network [Schöpf et al., 2011] were proposed. The caudate forms part of fronto-striatal processing loops subserving executive functions [Alexander, 1986] and was specifically ascribed to be involved in the selection of appropriate responses and their monitoring during performance of the ToL [Dagher et al., 1999].

CONCLUSION

The present quantitative meta-analytic evidence empirically substantiates the common notion of the crucial contribution of the dlPFC to planning in the ToL and further pinpoints it to be specifically focused on its mid-dorsolateral part. Furthermore, instead of a unilateral involvement, results highlight the bilateral contribution of left and right mid-dlPFC to planning on the ToL. In this regard, findings from previous studies converge on suggesting that the differential involvement of the left and right mid-dlPFC may be invoked by specific sub-processes of planning. However, the present methodological approach does not allow addressing this assumed process-dependent relative lateralization. Therefore, future studies have to explicitly investigate and identify these sub-processes so as to disentangle the differential roles of the left and right mid-dlPFC in human planning and thereby contribute to a comprehensive understanding of the general role of the PFC in complex cognitive functions. Apart from the mid-dlPFC, a range of further frontal (e.g., rostral PFC, FEF, SMA), parietal (e.g., IPL, precuneus), and opercular regions (anterior insula) are significantly involved in planning performance. In this respect, extending the focus of the present meta-analyses on mid-dlPFC toward its interaction with these other planning-associated brain areas may constitute a promising avenue for further research on the neural basis of complex cognition.

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