An fMRI-Investigation on the Neural Correlates of Tool Use in Young and Elderly Adults

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ABSTRACT

Using a key to open a door, a pen to write a letter or a fork for eating are actions we perform during our daily life. A wide range of different processes take place enabling us to perform these actions and to use objects as tools: We have to recognize the object, understand its functional purpose, know how to use it as a tool, grasp it and control the movement in order to achieve the intended goal. Analysis of the neural correlates of these processes in real actions with the help of functional magnetic resonance imaging (fMRI) is a challenging task considering the methodological circumstances, but can give a valuable insight into a brain process of an essential element of human daily life. The development of a new device suitable for the MRI environment, called "Tool-Carousel", made it possible to introduce real objects in the MRI scanner and measure brain responses during the planning and execution of real actions. The main goal of this thesis is to characterize the brain network responsible for processing real object manipulations and tool use. This includes not only the analysis of young adults, but also elderly individuals to evaluate age-related changes in the brain network responsible for actions with tools. Additional insight into the neural processes of tool use is given through a literature review. The latter covers fMRI studies of healthy adults and lesion analyses of patients with left brain damage suffering from apraxia. The connection of results from experimental studies on young and elderly individuals and the literature review lead to several conclusions characterizing the brain network responsible for tool use actions: The tool-specific network which processes tool use actions and the conceptual understanding of tool use is mainly left-lateralized, independent of both the hand used in the action and of age. Brain areas recruited during planning and execution overlap and include the ventral stream, parietal and frontal areas which are also shown to be affected in patients with tool use impairments. Both ventral and dorsal processing streams are involved in actions. The latter can be subdivided into two functionally separated pathways dependent on the involvement of semantical information involved in the action. Furthermore, it can be stated that age-related neural changes also affect the neural network processing real actions and mainly lead to activation increases during action planning and a compensatory mechanism in elderly individuals. Such aging effects in the tool use network should be considered in the analysis of patients with brain damage and tool use impairments that are in the same age group. Overall, this thesis provides new insights of brain function and an enhanced understanding of real actions, especially tool use, linking experimental studies with different age groups and a literature review of healthy adults and patients with impairments in tool use actions.

OVERVIEW

This thesis is divided into five chapters. The first chapter gives a general introduction into the main topic including the neural correlates of different aspects of tool use, neural changes in aging and tool use impairments in brain damaged patients with apraxia. A summary of the main goals of this thesis can be found at the end of the first chapter.

The next three chapters contain the reports of two experimental fMRI studies (chapter two and three) and a literature review (chapter four) in the form of research articles. The articles in chapter two and four are published and included in the format they were published in the journals. The research report in chapter three is so far unpublished and presented as a manuscript. A short introduction to all studies and the contribution of the author of this thesis are given in the beginning of each chapter.

The article presented in chapter two reports an fMRI study with healthy young participants measuring the neural correlates of real functional and transport actions with known tools and neutral unknown objects. The second manuscript included in chapter three uses the same method as the previous article and focusses on age-related changes in the neural correlates of real actions and compares the results from young and elderly adults. The last article in this thesis is presented in chapter four and contains a literature review on the impairments in actions of daily living in patients with brain damage. Furthermore, it summarizes results from fMRI studies of healthy adults and lesion analyses of patients to get a further understanding on the neural correlates of tool use and actions of daily living.

The last and fifth chapter of this thesis covers a general discussion of the findings from the experimental projects and the review. It aims to connect all three studies to draw general conclusions about the neural correlates of tool use which are then related to the current literature. Methodological limitations, potential improvements, future research possibilities as well as a general conclusion are also discussed.

CONTENT

1 Introduction – Tool Use in the young, elderly and damaged Brain

Human tool use is an important part of our daily life, with a widespread neural basis which can be influenced by healthy aging and brain damage.

Human tool making and tool use dates back around 2.5 million years and included the handling of hammering stones to produce sharp-edged stones for cutting and modifying other materials like bones or wood (Semaw, 2000). These simple tools enabled our ancestors to extend the selection of reachable food and possibly increased the access to food resources with higher quality (Ambrose, 2001). Along with the development and improvement of stone tools the increase of brain size was part of human evolution (Ambrose, 2001; Stout, Toth, Schick, & Chaminade, 2008; Wynn, 2003). Even though tool use is not a unique ability of the human being and has been reported in monkeys and more animal groups including other mammals, birds and even insects (Bentley-Condit, 2010), it can be clearly stated that no animal has trained, developed and improved this skill like the human being has done it. Enhanced hand-eye coordination, the development of handedness for improved fine-motor precision in the dominant hand and increased executive control of actions enabled the human being to perform complex object manipulations. Additionally, the development of causal reasoning, the formation of representations for object functions as well as social learning and teaching are some relevant abilities the human being developed in comparison to other animals which made it possible to establish the skill of using an object as a functional tool (Vaesen, 2012). Today, tool use is much more than using a stone for hammering. We open doors with a key, eat with fork and knife or sign a letter with a pen. These actions are performed during our daily life naturally without conscious thoughts on each part of the movement. Nearly intuitively we form our hand and fingers to grasp a certain object, lift and move it in order to help us to achieve our intended goal. In the end the object becomes a functional tool. Even though most of the common actions of daily living and tool use seem simple to us, the underlying processes behind such actions are multifaceted and include a variety of different steps. In order to illustrate the complexity of tool use, an introduction to the elements of such complex actions and their neural basis will be given in this chapter. Additionally, the neural and behavioral changes during healthy aging but also the neuroanatomical correlates of tool use in patients suffering from apraxia will be presented. Furthermore, the given information is put into context with the goal of this thesis.

The basic elements of Tool Use and their neural underpinnings

Using a tool is a complex action and includes a variety of sub-actions and processes. One crucial part of tool use is the recognition of an object as a tool and therefore associating it with a meaning, functionality and usage (Menz, Blangero, Kunze, & Binkofski, 2010; van Elk, van Schie, & Bekkering, 2014). Furthermore, the accurate motor plan has to be created and the proper hand and arm posture formed in order to be able to reach for and grasp the tool properly (Randerath, Goldenberg, Spijkers, Li, & Hermsdörfer, 2010; Vingerhoets, Nys, Honoré, Vandekerckhove, & Vandemaele, 2013; Vingerhoets, 2014). Next, the motor plan has to be actually executed including the tool specific movements which during the execution have to be monitored and potentially corrected (Gaveau et al., 2014; Rizzolatti & Matelli, 2003). These are essential components of goal directed actions with tools and these processes will be referred to as elements of tool use in this thesis.

On a neural level these elements can be separated in and attributed to specific neural circuits. Several scientific methods can be used for this purpose including functional and structural MRI, transcranial magnetic stimulation (TMS) and lesion analyses with brain damaged patients. MRI is a valuable method to acquire insight into the brain's structure and function with a high spatial resolution. While structural MRI gives information about anatomical composition of the brain, fMRI can give further insight into dynamic processes and task dependent brain mechanisms. FMRI makes it possible to associate an anatomic location of the brain to function and helps to characterize networks responsible for certain processes and behavior (Friston, 2009; Raichle, 2009). It is an indirect measure of neural activity and is based on haemodynamic changes in brain areas. The blood-oxygen-level-dependent (BOLD) response is the signal measured and depends on the effect that neural activity causes a regional increase in the cerebral blood flow, over-compensating decreases in oxygen and leading to increased supply of oxygenated blood. Contrasting the measured signal of different tasks makes it possible to map the brain locations which are responsible for a certain function (Logothetis, 2008). FMRI is a non-invasive method which measures heamodynamic processes in relation to cellular activity, other methods like TMS or lesion analyses are based on selective magnetic stimulation of the brain or the analyses of damaged brain tissue due to neurological incidents, respectively. Both TMS and lesion analyses use the approach to analyze behavioral changes caused by alterations or stimulations of particular brain areas and therefore conclude links between brain areas and specific functions (Miniussi & Ruzzoli, 2013; Rorden & Karnath, 2004). Despite the different approaches, all methods provide information about the brain's function and can help to characterize the neural network responsible for tool use.

In the following paragraphs the elements of tool use are presented and associated with different brain areas based on different methodological approaches described above. This includes the topics of object recognition, knowledge of function and manipulation, reaching, grasping and the online control of actions. Additionally, different experimental methods and studies that aim to study tool use as a whole process are summarized. The final two paragraphs take all elements of tool use together and show possible connections to present a model characterizing the tool use and action network. Figure 1 visualizes the reported findings and assumptions summarized below.

The ventral stream and object recognition

Clearly, before an object can be used as a tool it has to be seen and recognized. The neural pathway generally believed to have a central role in this process is the ventral stream (Goodale & Milner, 1992; Milner & Goodale, 2008). It is a functionally specialized and hierarchically organized structure, analyzing basic visual stimuli and integrating this information for the recognition of several different object categories (Grill-Spector & Malach, 2004). On a neuroanatomical level, the ventral stream reaches from the striate cortex including the primary visual areas to the temporal cortices, covering also the fusiform gyrus and structures like the lateral occipital complex (LOC) (Grill-spector, Kourtzi, & Kanwisher, 2001; Grill-Spector & Malach, 2004). With respect to the functionality of the mentioned brain areas of the ventral stream, they seem to be specialized for the recognition of specific stimuli. The occipital and fusiform face area show a specificity for faces (Kanwisher, Tong, & Nakayama, 1998), the parahippocampal area for places (Epstein, Harris, Stanley, & Kanwisher, 1999), the extrastriate and fusiform body area for bodies (Downing, Jiang, Shuman, & Kanwisher, 2001; Peelen & Downing, 2007), the LOC for objects (Grill-spector et al., 1999) and the posterior middle temporal gyrus (pMTG) specifically for tools (Lewis, 2006). Considering the specification of the LOC and pMTG it is clear that both brain areas play a key role in the process of using a tool. Brain imaging studies have shown that across different tasks, which require the retrieval of semantic object information and object properties, temporal brain areas (especially the pMTG) (Chao & Martin, 2000; Chao, Haxby, & Martin, 1999) as well as the LOC (Monaco et al., 2011; Vingerhoets, 2008) are recruited.

Object function and knowledge of object manipulation

The recognition of an object does not directly enable us to use it as a tool. In addition to the object identity functionality also has to be associated with the seen object. Furthermore, an individual has to know how the object is used. After knowing that the object in front of us is called "hammer" we have to recall that a hammer is used to push a nail into a wall. Additionally, we have to know that the hammer has to be moved forward and backward hitting the nail to achieve the intended goal. The first mentioned aspect is often referred to as "function knowledge", while the knowledge of the accurate movement is called "manipulation knowledge" (Buxbaum & Saffran, 2002; van Elk et al., 2014) and for simplification these terms will be used further on. Once we have learned the function of a certain object we associate it with this specific purpose or goal. This formed association leads to a phenomenon known as functional fixedness (German & Defeyter, 2000; German & Barrett, 2005; German & Leslie, 2001) a term that describes the assumption that acquired function knowledge makes it harder to detect other possible functions to achieve a certain goal not directly associated with the object. German and Leslie (2001) showed that functional fixedness is based on experience and learning. Younger children are able to use an object in an uncommon way to solve a problem, while older children with more experience and object-function associations struggle to overcome the effects of functional fixedness to use an object in an uncommon way (German & Leslie, 2001). When the association between object and function is made, the knowledge of how the tool is manipulated is an additional aspect which is essential for proper tool use. The embodied cognition hypothesis argues that the conceptual understanding of an object (including function knowledge) is inseparable of the sensory-motor system and the manipulation knowledge of an object (Gallese & Lakoff, 2005). It claims that the neural simulation of action is necessary to comprehend knowledge about function. Considering the large set of neural imaging studies showing co-activated brain patterns of perceptual, associative and also sensory-motor related brain areas during viewing, naming and imagining tool use actions (Lewis, 2006), the embodied cognition hypothesis seems plausible. On the other hand, the assumption that the function knowledge and manipulation knowledge are actually two separate elements of tool use and are associated with different neural networks has been proposed in a variety of studies also (Buxbaum & Saffran, 2002; Garcea & Mahon, 2012; Negri et al., 2007; Sirigu, Duhamel, & Poncet, 1991). A dissociation of the two information types was shown through neurophysiological observations in patients suffering from apraxia and fronto-parietal lesions after a stroke. In those patients, manipulation knowledge was impaired, while function knowledge was preserved. In the same study a group of stroke patients not being diagnosed with apraxia on the other hand showed impaired function knowledge (Buxbaum & Saffran, 2002). A behavioral study with healthy individuals confirmed the assumption that function knowledge and manipulation knowledge of objects are two distinct types of object information, showing that judgments about object functions do not need the simulation of object manipulation (Garcea & Mahon, 2012). In functional imaging studies this idea of separating function and manipulation knowledge is analyzed also with respect to the neural correlates for each concept. While the representation of manipulation knowledge of an object was found to be associated with activations in inferior parietal lobe, specific brain areas coding function knowledge could not be identified in the studies of Boronat et al. (2005) and Kellenbach, Brett, and Patterson (2003). Another study by Canessa et al. (2008) verifies the assumption and shows, next to parietal activations and additional frontal activations representing manipulation knowledge, a relevance of temporal regions for processing function knowledge. Equivalent results were reported by different TMS studies which demonstrate that stimulation of the inferior parietal cortex affects decisions about manipulations, while decisions about functions are not derogated. Stimulation of the temporal cortex on the other hand had the opposite effect (Ishibashi, Lambon Ralph, Saito, & Pobric, 2011; Pelgrims, Olivier, & Andres, 2011; Pobric, Jefferies, & Ralph, 2010).

In summary, function knowledge and manipulation knowledge and their neural correlates seem to be separable and represent two distinct types of object information. Function knowledge is mostly associated to the temporal cortex, while manipulation knowledge is connected with inferior frontal and parietal recruitment. Especially the characterization of manipulation knowledge in tool use and its form of representation in the brain is debated and will be a topic of discussion in chapter 5 of this thesis.

Reaching and grasping

In the case of manually used tools the functional object has to be reached for and grasped, in order to be moved and manipulated. The arm and hand have to be moved towards a target and the hand position and shape has to be adjusted dependent on the objects form and function. Reach-to-grasp movements are based on visuomotor integrations and the neural brain regions include a variety of mainly parietal brain areas. Evidence for the localization of reach-related brain areas can be provided by neurological observations of patients suffering from optic ataxia, a component of the Balint`s syndrome (Bálint, 1909). These patients show impaired reaching movements and are not able to move arm and hands properly to reach an attended goal. Generally these observations cannot be explained simply by primary sensory or motor impairments. Lesions in the posterior part of the parietal lobe are usually the reason for the mentioned deficits (Andersen, Andersen, Hwang, & Hauschild, 2014). Different studies overlapping the lesion sites of patients with impaired reaching movements show the strongest lesion overlap in the superior parietal lobe (SPL), the intraparietal sulcus (IPS) and also at the junction between the SPL and parts of the occipital cortex extending to the precuneus (Karnath & Perenin, 2005; Perenin & Vighetto, 1988). Research using fMRI focused on reach-related brain activation as well and found similar results emphasizing the importance of the posterior parietal cortex in reach-to-grasp actions. Overall the activations are detected in both hemispheres and include a variety of brain sites like the posterior part of the intraparietal sulcus as well as more anterior sites of the IPS (midIPS) (Gallivan, McLean, Valyear, Pettypiece, & Culham, 2011). An area located at the border between the parietal and occipital lobe around the parieto-occipital sulcus called the superior parieto-occipital cortex (SPOC) also close to the parieto-occipital sulcus (POS) (Gallivan, Cavina-Pratesi, & Culham, 2009) is of importance, too. TMS studies can verify such findings and demonstrate an effect on reaching after stimulating parts of the posterior parietal lobe and especially SPOC and IPS (Desmurget et al., 1999; Vesia, Prime, Yan, Sergio, & Crawford, 2010). Brain areas relevant for processing grasping movement are located in close proximity of the reach-related sites and also include similar structures like the IPS. Especially the anterior part of the intraparietal area (AIP) (Borra et al., 2008; Jacobs, Danielmeier, & Frey, 2010; Rice, Tunik, & Grafton,

2006) has often been reported as being relevant for grasping. While in monkeys reaching and grasping seem to be processed in two different pathways, a dorsomedial one for reaching and a dorsolateral one for grasping, there does not seem to be the same clear separation in humans (Turella & Lingnau, 2014). Gallivan et al. (2011) demonstrated that brain areas which can be associated with the dorsomedial reaching circuit (SPOC and midIPS) show relevance for planning grasping movements compared to touch movements (including reaching movements only). Additionally, the aIPS, as well as the dorsal and ventral premotor areas, show a similar relevance in this study. Therefore, the location of reach- and grasp-related brain areas are not only limited to the parietal lobe. Frontal areas like the dorsal and ventral premotor cortex (PMd and PMv) also show involvement in visually guided reaching and grasping. The PMv seems to be more relevant for pre-shaping the hand for grasping and the PMd for simpler lifting tasks (Davare, Andres, Cosnard, Thonnard, & Olivier, 2006). It also has to be noted that the described brain network processing reaching and grasping seems not only important for planning such movements but also monitors the online control of the action (Gaveau et al., 2014). Therefore another possible hypothesis argues that mistakes during reaching and grasping movements after posterior parietal lesions occur because of an inability to correct and adjust movement errors (Andersen et al., 2014). Healthy individuals can adjust their reaching behavior when the intended target is moved during the reaching act, while a patient with the lesions described previously is not able to modify the movement (Gréa et al., 2002; Milner et al., 2001; Pisella et al., 2000).

Looking at studies on reaching and grasping movements in object manipulations and tool use, a similar pattern of activations can be observed. Especially the anterior part of the IPS is not only important for grasping objects in general, but seems to be of great relevance for grasping tools in particular. The activation level in this area is higher for tools than for graspable objects (Valyear, Cavina-Pratesi, Stiglick, & Culham, 2007) and is also associated with representation of the use-specific object goals during object grasping (Vingerhoets et al., 2010). Next to the aIPS, the PMv also seems to be particularly important for grasping usable objects (Jacobs et al., 2010) and for matching the position of the hand and fingers in relation to the objects' properties and function (Vingerhoets et al., 2013).

In summary, the superior and posterior parietal cortices are strongly involved in reaching and grasping movements as well as the online control of actions. Premotor areas are additionally relevant for the selection of correct hand shapes and postures. A special relevance in grasping tools for their functional use lies in the anterior IPS and the PMv.

Multiple ways to analyze Tool Use

Due to the relevance of object manipulation in our daily routine it is reasonable that the execution of tool use as a whole action and not only the aspect of recognition, recalling function, reaching and grasping is of interest in brain imaging studies. Caused by the specific methodological conditions in an MRI scanner, the analysis of real actions and tool use is rather difficult: The bore of an MRI scanner is large enough to lie in for an average sized adult, but not to perform large far-reaching arm movements. Additionally, all movements have to be restricted to a minimum in order to avoid head motion which can lead to artifacts in the acquired fMRI data. A lot of tools in daily life contain metal parts and therefore cannot be used in the MRI. Furthermore, the presentation of real objects, which are in reach and usable for a participant during an experiment, cannot be arranged in the scanner room easily while participants are lying in the MRI. Therefore, not many studies confront these difficulties and experiments including real tools and movements are rare.

Very prominent paradigms to study the brain areas related to tool use in an alternative way are the imagination, observation and imitation of real actions, because it can be assumed that the engagement of tool-related actions without tools show similar brain activations as the real action with tools. Even though manipulating an object with the hands is a motor task, the neural resources needed for the execution usually activate during the observation or imagination of actions without any movement involved. As expected, the observation and the imagination of tool use recruit brain areas similar to the ones described before, but the results of both tasks do not overlap and show variations (Wadsworth & Kana, 2011). Imitating an action instead of just imagining or observing it represents a closer substitute of real tool use (Manthey, Schubotz, & Cramon, 2003; Niessen, Fink, & Weiss, 2014; Weiss et al., 2006). A meta-analysis summarizing literature of fMRI studies focusing on observed and imitated actions revealed that while the known fronto-parieto-temporal network is associated with both tasks, some other brain areas like the left ventral premotor cortex and right ventral stream areas, frontal and sensorimotor cortices are increasingly relevant in the imitation tasks compared to the observation tasks (Caspers, Zilles, Laird, & Eickhoff, 2010). Additionally, the imitation of hand actions with an object compared to actions without an object (for example, imitation of meaningless finger and hand movements) recruit similar frontal and parietal areas, while ventral stream areas additionally associated with the imitation of object related actions.

The imitation of object manipulations can also be referred to as pantomime of tool use. Brain imaging studies analyzing pantomime of tool use often compare tool use gestures with meaningless hand gestures or hand movements and usually find a brain network including most of the brain areas described previously (Choi et al., 2001; Johnson-Frey, Newman-Norlund, & Grafton, 2005; Moll et al., 2000; Rumiati et al., 2004): Ventral stream areas like the pMTG and lateral occipital areas processing semantic and visual object properties, parietal areas including the SPL and IPS associated with monitoring action related hand and arm movements for reaching and grasping (in case of the aIPS especially for tools) as well as the supramarginal gyrus (SMG), which is also shown to be activated during tool observation and is related to processing action semantics (Chao & Martin, 2000; Peeters, Rizzolatti, & Orban, 2013). Frontal brain activations including the ventral and dorsal premotor area for motor representations of tool related actions are also detected during the pantomime of tool use gestures. Even though the pantomime of object manipulation is a valuable method for analyzing tool use, it is clear that there are differences between both tasks. Obviously, tool use pantomime misses one major aspect of tool use: the tool in the hand. It can be assumed that the missing sensory feedback has an influence on the neural process of the action. Without perception of the actual intended goal and its achievement, the online control mechanism of an action will not be recruited as it would during real actions. It can be assumed that a pantomimed tool use gestures will never be as accurate and natural as an action with real tools and intended goals. Differences between the neural correlates of the pantomime of actions and real actions have been observed in a study on grasping movements, showing that the key area in this task is significantly stronger activated during real actions (Króliczak, Cavina-Pratesi, Goodman, & Culham, 2007). In another study comparing tool use pantomime and the real use of tools, major differences can be found mainly during the execution, including the expected primary sensorimotor cortices as well as temporal, posterior parietal and frontal lobe areas which are all part of higher cognitive aspects of motor control (Hermsdörfer, Terlinden, Mühlau, Goldenberg, & Wohlschläger, 2007). The preparation of tool use acts and pantomime on the other hand showed very similar activation patterns.

As a result of these studies, covering different paradigms related to tool use actions, it seems that while all of them produce valuable information characterizing the tool use network, there are still variations in the results and differences compared to real actions. Only a few studies focused on the manipulation of real objects in the scanner environment and included for example the use of tongs as a tool to grasp a small object (Inoue et al., 2001), the imitation of tool acts with small sized tools (Valyear, Gallivan, McLean, & Culham, 2012), the manipulation of tools and objects including the adequate recipient (Hermsdörfer et al., 2007) and the use of a pair of reverse tongs for grasping (Gallivan, McLean, Valyear, & Culham, 2013). The latter study used a multi-voxel pattern analysis in order to decode the preparatory brain activations in a variety of relevant brain areas and detect if early brain responses can predict the upcoming action. The actions included reaching or grasping an object either with the hand or a tool (reverse tongs). The results strengthen many of the previously mentioned findings and associate the different brain areas with hand and tool actions. SPOC, for example, mainly codes actions with the hand, while the SMG and MTG are selective for actions with tools. The aIPS shows predictive activation for both tool and hand actions, but with distinguishable neural activation patterns. The pIPS, PMd and PMv, on the other hand, also code for both action types, but with similar neural activations. The authors subdivide the group of regions in two separate networks: One represents the fronto-parietal hand action network with reaching and grasping circuits including the more dorsal located brain regions associated with hand actions. The other network is located more ventral and is defined as the tool network including the MTG, SMG and PMv which are associated with tool actions (Gallivan et al., 2013). The studies including real actions and objects give the most accurate view on the neural correlates of tool use, but either miss visual feedback (Hermsdörfer et al., 2007), real sized tools (Valyear et al., 2012) or a variety of familiar goal-related actions with tools (Gallivan et al., 2013). Therefore, the previous body of research is missing the analysis of actual tool use with a variety of familiar tools known from daily life and the corresponding target object with visual feedback of the action.

One very common finding in the presented studies is the strong left-sided lateralization of the network relevant for tool use actions. It cannot be completely ruled out that the left-sided lateralization could also be associated with left-lateralized language-related activations especially during the imagination of tool use and pantomime. It is therefore important to analyze real actions and not only substitutes. Those studies including actual movements (Gallivan et al., 2013; Imazu, Sugio, Tanaka, & Inui, 2007; Johnson-Frey et al., 2005; Vingerhoets, Vandekerckhove, Honoré, Vandemaele, & Achten, 2011) observe the neural correlates while subjects use their dominant right hand. Left-sided activations cannot solely be traced back to the lateralization of the tool use network, but also to contralateral motor control. This bias can be avoided by using both hands (Hermsdörfer et al., 2007; Gregory Króliczak & Frey, 2009; Martin, Jacobs, & Frey, 2011; Moll et al., 2000). The structure and lateralization of the tool network during actual tool use dependent of the hand used in the action is not yet fully analyzed.

As it was shown in this paragraph, there are several studies aiming to analyze the neural correlates of tool use by including tasks similar to tool use. The results show overlapping results, but also variations in the activation pattern dependent on the used paradigm. Real actions with tools and actions of daily life routines in the MRI environment are still rare, but give the most accurate insight into the brain process of real tool use.

Summary of the elements of Tool Use

Taking together the presented literature we see that the manipulation and use of a known functional object includes a wide neural network with different separable processes which can be located in different functional subnetworks in the brain. The relevant brain locations and a brief description of their role during tool use are visualized in Figure 1. A basic principle underlying the neural organization of these goal directed actions with objects is the model of the two visual information processing pathways: The ventral stream, important for the recognition of objects and their features for planning behavior and the dorsal stream, relevant for controlling the manipulation of an object in space to execute actions (Milner & Goodale, 2008). Further analyses of organization of the dorsal stream lead to the hypothesis that the dorsal stream can be further subdivided in two action related streams on for acting on and the other for actin with objects (Binkofski & Buxbaum, 2013; Johnson & Grafton, 2003): The dorso-dorsal stream seems to be necessary for the online control of reaching and grasping movements and monitor an object manipulation dependent on the objects' orientation and structure (Gallivan et al., 2011; Milner et al., 2001; Pisella et al., 2000; Turella & Lingnau, 2014). The ventro-dorsal stream seems to be more relevant for the semantics of an action and learned object manipulations like tool use (Buxbaum, Kyle, Tang, & Detre, 2006; Frey, 2008; Kalénine, Buxbaum, & Coslett, 2010).

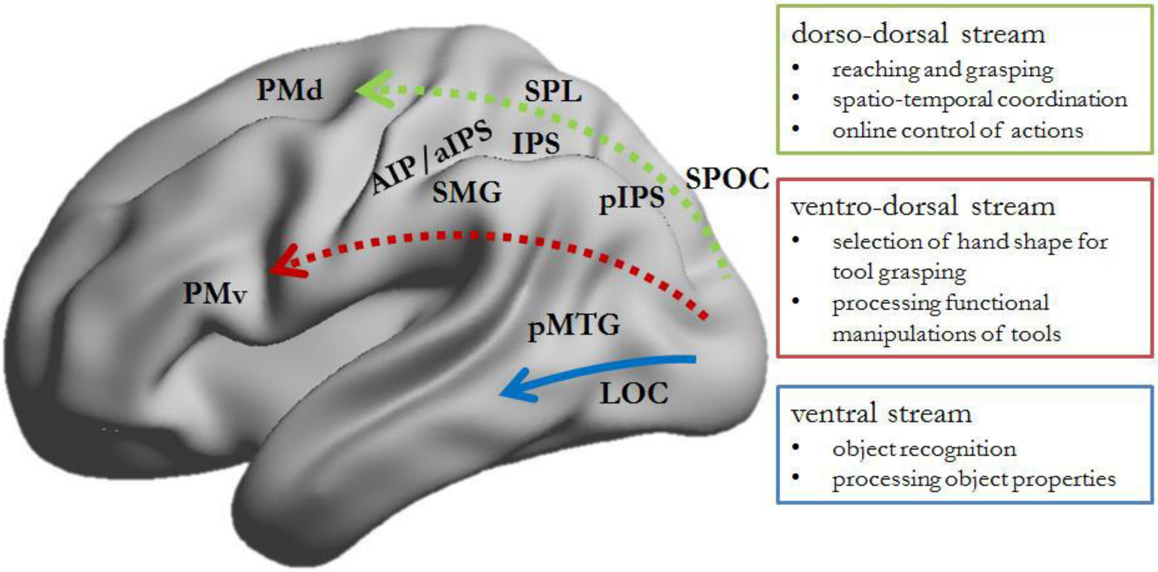

Figure 1: A model of the organization of the network relevant for tool use and actions. Shown are the dorso-dorsal stream in green, the ventro-dorsal stream in red and the ventral stream in blue on a rendered left hemisphere of the brain.

The separation of these two processing stream seems plausible, but further evidence is needed to see if this theory can be applied to real actions with objects and tools.

Connecting all elements of Tool Use

Most of the discussed studies focused on separating the functional subnetworks and attributing different brain locations to specific functions in the complete act of recognizing, understanding and performing the use of tools. An additional question is how all this different information, which has to be processed during the use of a tool, is integrated in order to use a tool in a functionally appropriate way. Clearly, it is not enough to recognize an object, its physical properties and function and to associate it with a functional movement. This information has to be passed on to another system which can integrate and transform it to shape the appropriate hand and arm movements. This means that tool use is not only dependent on local processes and the functionality in the grey matter of the brain, but also on the white matter fiber tracts which connect the different brain areas. This assumption can be strengthened by observations of patients with apraxia which show that flawless tool use does not only depend on the integrity of the grey matter tissue, but also on intact white matter (Randerath et al., 2010). With the help of structural connectivity analysis it is possible to get an insight into the connection of the subnetworks within the tool use network presented and show how the different information can be passed on.

On a structural level the connectivity of different brain areas can be analyzed with diffusion tensor imaging (DTI), a method which characterizes white matter tracks based on the direction of diffusing water molecules (Le Bihan et al., 2001). After characterizing brain areas sensitive to correct hand postures as well as semantically appropriate tool use, Hoeren et al. (2013) demonstrated that the connections of the functionally separated parietal and frontal areas are based on two dorsal fiber tracks. This result underlines the existence of strong connections for the integration of action relevant information. Such parieto-frontal connections are also found in a different connectivity analysis on object grasping. Here, information about the object and grasping movement is processed along the two dorsal streams from a visual region to parietal centers ending in two premotor areas (PMv and PMd) (Grol et al., 2007). With regions of interest based on the study of Frey et al. (2005) on tool use pantomime, Ramayya, Glasser, & Rilling (2010) also analyzed the structural connections within the tool use network. They found different left-lateralized pathways connecting the MTG with the posterior SMG/angular gyrus, the MTG with the anterior SMG as well as the anterior SMG with the frontal cortex (premotor area). The authors argue that connections from the MTG to the SMG are relevant for the integration of conceptual and semantic object properties with visuospatial information of the environment to create a plan to grasp a tool for its functional use. The connection from these parietal regions to the frontal lobe is thought to process the transformation of the conceptual plan of tool use into a real motor action (Ramayya et al., 2010).

In summary, these studies show that the brain areas which are active during tasks related to tool use are also connected on a structural level forming a linked fronto-parieto-temporal network. Within such a connected network information about an object and the related manipulations can be integrated and connected in order to grasp and use an object as a functional tool to achieve an intended goal.

The Impacts of Healthy Aging on Tool Use

The research on the elements of tool use and their neural representations give a valuable insight into a relevant process of our daily life routine. One aspect and possible influence was not taken into consideration so far: the factor aging. We start to learn how to use tools when we are very young. Already infants start to pay attention to properties of tools and their causal effects, connect functions to objects by observing actions by others and imitate meaningful tool actions (Hernik & Csibra, 2009). We increase our fine motor skills and our tool use expertise during our development when we become adults and the act of using a fork and knife or turning a key in a lock becomes a natural action we do not control and monitor consciously. It happens intuitively and in healthy adults usually without problems and disturbances. But what happens to our ability to use objects as functional tools to interact in our environment when we get older?

On a behavioral level, several aspects in the motor performance of an action seem to be affected by age-related changes. In general, elderly individuals above 60 years of age show an overall deficit in the coordination of movements and the alterations are seen in bimanual actions including multi-joint movements especially (Seidler, Alberts, & Stelmach, 2002). Furthermore they show higher variability of movements (Contreras-Vidal, Teulings, & Stelmach, 1998), a decreased speed of actions and movements (Ren & Wu, 2013) and a general deficit in the visuomotor control system avoiding errors (Heenan, Scheidt, Member, Beardsley, & Member, 2014). Elderly adults, 65 years of age and older, are also affected in the temporal and spatial coordination of motor actions with both hands (Stelmach, Amrhein, & Goggin, 1988; Wishart, Lee, Murdoch, & Hodges, 2000). Concerning simple grasping movements, elderly individuals show differences in kinematic aspects of a movement including significantly lower grip force than younger adults (Lin et al., 2014) and higher variability in the control of force especially during grip release (Voelcker-Rehage & Alberts, 2005). The analysis of grasping usable objects known from daily life is more closely related to tool use. Cicerale, Ambron, Lingnau, and Rumiati (2014) compared several kinematic parameters of young (19 - 25 years old) and elderly adults (65 - 75 years old) while they had to plan and execute grasping movements. Participants had to grasp usable objects dependent on the action goal, meaning either grasping the object for transportation or for use. Additionally, the object´s properties including size, orientation in space and location in the visual field was altered. Elderly did not show longer movements, but several other parameters differed between the groups. The general pattern of movement characteristics including an increased time for approaching the target, an increased grip aperture and less wrist rotation, was altered in the elderly. The accuracy of grasping was impaired also, but only with decreased visual feedback when the object was not in the central visual field. A possible reason for these behavioral changes is neural atrophy causing alterations in the neural network processing these actions.

Age-related brain volume decline during healthy aging has been reported multiple times (Courchesne et al., 2000; Good et al., 2001) and relates to behavioral changes in different cognitive and motor processes (Seidler et al., 2010). The loss of grey matter volume is most strongly examined bilateral in the parietal lobe, post- and precentral gyrus, the insula cortex and anterior cingulate cortex (Good et al., 2001). In the same study grey matter volume decline is also found in the left middle frontal gyrus and parts of the temporal lobe in both hemispheres. Less atrophy was measured in subcortical areas. Other studies find the strongest grey matter decline in the prefrontal cortex including dorsolateral prefrontal cortex and orbitofrontal cortices (Raz et al., 2004; Salat et al., 2004). Temporal and occipital brain areas seem to be less affected by age-related neural atrophy (Good et al., 2001; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Next to the grey matter decline, also white matter volume declines during aging, but at a later time point at age 70 - 80 years (Courchesne et al., 2000; Ge et al., 2002). Again, prefrontal areas show the highest decline in volume compared to the rest of the brain (Salat et al., 2005). Therefore, several brain regions belonging to the tool use network are affected by age-related atrophy. With this in mind, changes in the different aspects of tool use and motor performances seem to be reasonable.

Overall, we see several behavioral age-related changes which go along with alterations of the neural processing in the brain. Previous neuroimaging research on different cognitive domains in healthy elderly adults showed that activation patterns are usually more bilateral and widespread in elderly compared to young adults (Cabeza, 2002; Grady, 2012). A meta-analysis comparing the neural changes due to healthy aging in different cognitive tasks demonstrated that the strongest differences between young and elderly can be found in anterior brain regions including parts of the prefrontal cortex which mainly show higher activations in elderly individuals (Spreng, Wojtowicz, & Grady, 2010). The authors also note that the pattern of over-activated brain areas in the elderly is strongly dependent on the performance and differs, if the performance of elderly in the tested task is the same or worse compared to the young participants (Grady, 2012).

Looking at neural changes in visual or semantic tasks due to aging, alterations in face processing with neural changes in the fusiform face area (Lee, Grady, Habak, Wilson, & Moscovitch, 2011) and also during object processing with changes in neural responses in the LOC can be reported in elderly adults (Chee et al., 2006; Goh et al., 2007). Another study on semantic processing of objects, evaluating age-related changes in the neural representations of object concepts and knowledge of visual properties of the object, found activations of temporal and frontal brain areas in young and old adults during the task (Peelle, Chandrasekaran, Powers, Smith, & Grossman, 2013). Differences were found after separating the elderly cohort in two groups based on their performance in the task. Elderly individuals who performed well showed an increase in activation strength in the premotor cortex in both hemispheres and the left LOC. Those older participants with decreased activity in the anatomic locations mentioned above also showed decreased performance.

In the motor domain research also found that elderly show an overall increase of brain activation and recruit additional brain areas compared to young adults to perform a motor task (Heuninckx, Wenderoth, Debaere, Peeters, & Swinnen, 2005; Heuninckx, Wenderoth, & Swinnen, 2008; Mattay et al., 2002; Noble, Eng, Kokotilo, & Boyd, 2011; Ward, 2003; Ward, Swayne, & Newton, 2008). Heuninckx et al. (2008) showed that during flexion-extensions of hands and feet elderly participants recruited an extended network compared to young adults including stronger activations in inferior frontal, superior temporal region, the SMG and fusiform gyrus. Studies performed by Ward et al. (2003, 2008) show a comparable effect during a simple isometric grasping movement with the dominant and non-dominant hand. Additional recruitment was found especially in the left hemisphere independent of the used hand. Other studies observing grasping actions in elderly adults underline these findings and also show an increased activation level for example in the PMv (Noble et al., 2011). A structural age-related change in the organization of brain networks during grasping movements was also found in particular during actions with the non-dominant hand (Park, Boudrias, Rossiter, & Ward, 2012). Another prominent effect of healthy aging is the reduction of selectivity in the elderly brain. Especially the visual system activates less differentiated for different stimuli in the elderly compared to young adults (Grady et al., 1994; Grady, 2002). Park et al. (2004) showed that ventral stream areas, which are selectively active for the different stimuli in young adults, are less specified in elderly adults. Similar results can be found in other cognitive domains during explicit and implicit learning tasks (Dennis & Cabeza, 2011) but also in the motor domain during a finger tapping task (Carp, Park, Hebrank, Park, & Polk, 2011).

Taken together, two major findings can be observed in the neural process of aging in general: One is characterized by an over recruitment of brain areas, while the other is connected to decreased selectivity of brain areas dependent on different tasks or stimuli. In order to explain this age-related phenomenon, two theories developed: The compensatory theory attributes the age-related changes and increased brain activations to a compensatory mechanism ensuring good performance in elderly (Grady, 2012; Heuninckx et al., 2008; Ward, 2006). The other theory believes that unspecific brain activations in elderly are due to a general dedifferentiation in the neural system and are associated with a decreased connection between function and location of specific brain areas (Carp et al., 2011; Dennis & Cabeza, 2011; Grady, 2012). If a compensatory mechanism is present in the neural processes of tool use, or if the tool use network shows dedifferentiation effects is not yet clear. While the findings about age-related neural alterations and the theories help to get a better understanding about what happens in the aging brain, research on aging effects on the process of tool use and object manipulation is still missing. Apart from increasing the general understanding of the age-related changes of the tool use network in elderly adults it also enables a closer comparison to clinical observations of patients with lesions which are of higher incidence in higher age.

Tool Use and Apraxia

Impaired tool use is closely linked with the term apraxia. It describes a variety of symptoms and is caused by brain lesions mainly in the left hemisphere. These particular lesions result in deficits in executing motor actions including the imitations of meaningless gestures, communicative gestures, the pantomime of tool use and actual tool use (Buxbaum, Giovannetti, & Libon, 2000; Goldenberg & Hagmann, 1997; Goldenberg & Spatt, 2009; Goldenberg, 2008; Hermsdörfer, Li, Randerath, Roby-Brami, & Goldenberg, 2013; Randerath et al., 2010; Weiss, Rahbari, Hesse, & Fink, 2008). Originally the concept of apraxia has been formulated by Hugo Liepmann in 1908, who believed that apraxia is a movement disorder in which the plan and idea to conduct an action and its actual motor execution is disconnected, leading to impaired motor actions. In general apraxia can be characterized by impairments of skilled movements including gestures and tool use but which are not based on a disorder of the primary sensory or motor system (Rothi & Heilman, 1997).

As mentioned above, apraxia is associated with deficits in the execution of specific actions. The exact pattern of behavioral impairments vary across patients including different performance levels in the actions (gesture production, pantomime, actual tool use) usually impaired in apraxia (Goldenberg, 2014). Based on these differences already Hugo Liepmann characterized different types of apraxia: "Ideational apraxia" is usually associated with impaired tool use actions and the inability to use the correct tool for a certain goal. The term "Ideo-kinetic apraxia" which is also referred to as ideomotor apraxia, is mainly associated with an impaired ability to pantomime tool use and imitate meaningful and meaningless gestures. While these patients are not able to pantomime, for example, the use of a spoon properly they show less impairment with the real objects in their hand. Patients with "Limb-kinetic apraxia" on the other hand are usually able to perform tool use actions in a conceptual correct way but are not able to conduct smooth and precise movements as healthy individuals would do (Bieńkiewicz, Brandi, Goldenberg, Hughes, & Hermsdörfer, 2014; Goldenberg, 2008). In relation to the elements of tool use described previously it can be seen that all of these, including conceptual and semantic aspects like function knowledge and knowledge of object manipulation as well as action related elements like reaching, grasping, execution and the online control of actions, can be impaired in apraxia and depend on the integrity of different segregated brain regions.

The diversity of behavioral deficits in apraxia is similar to the diversity in the lesion location observed in patients. In general, lesions of the left brain are associated with symptoms related to apraxia and the areas affected can cover the parietal, frontal and temporal lobe (Goldenberg, 2014). Which lesion locations lead to which behavioral pattern of apraxia, is not jet fully understood. Voxel based symptom lesion mapping (VSLM) is a method which can give further insight into associations between the location of a lesion and the behavioral deficit which is caused (Rorden, Karnath, & Bonilha, 2007; Rorden & Karnath, 2004). Such analysis with anatomical data of patients with apraxia is therefore another possibility to characterize the brain areas relevant for tool related actions. Lesion analyses on impaired gesture imitation revealed an association between damages in the inferior parietal and frontal lobe of the left hemisphere and deficits in creating correct hand and finger positions (Goldenberg & Hagmann, 1997; Goldenberg, 1996;

Goldenberg, 2014; Buxbaum, & Moll, 2006; Weiss et al., 2001; Weiss et al., 2014). Right brain damages can lead to similar impairments also, but less severe and less frequently (Goldenberg, 1996; Weiss et al., 2001). The imitation of meaningless gestures in particular is found to be caused by lesions of the parietal lobe including posterior parietal regions (Hoeren et al., 2014) as well as inferior parietal lobe which lead to the conclusion that the spatio-temporal organization of movements is strongly dependent on the parietal cortex especially with increased action complexity (Weiss et al., 2001). Lesion analyses of tool use pantomime showed different findings concerning the most relevant lesion sites. In some studies the integrity of the inferior frontal gyrus and insula seems to be of most relevance for intact performance (Goldenberg, Hermsdörfer, Glindemann, Rorden, & Karnath, 2007; Hermsdörfer et al., 2013; Manuel et al., 2013), others show additional relevance of parietal and temporal brain locations for tool use pantomime performance and recognition (Buxbaum, Kyle, & Menon, 2005; Buxbaum, Sirigu, Schwartz, & Klatzky, 2003; Hoeren et al., 2014; Kalénine et al., 2010; Niessen et al., 2014). The impairment of real tool use is associated with similar frontal (Hermsdörfer et al., 2013) and parietal (Goldenberg & Spatt, 2009) regions while the retrieval of functional knowledge of tools can be related to temporal areas (Goldenberg & Spatt, 2009).

Overall, the lesion analyses with patients demonstrate that correct performance of different hand and tool related actions are dependent on a fronto-parieto-temporal network. It has to be stated though that the findings and exact lesion patterns vary across studies and that the neuroanatomical basis of apraxia is therefore not fully clear yet.

Aim of the Thesis

The main goal of this thesis is to investigate the neural underpinnings of real tool use under utmost realistic conditions. The method of fMRI is used because it provides a non-invasive method to study brain function during an action or task in healthy individuals and enables the association of neuroanatomical locations to a specific function. With this method, the analysis and characterization of the neural network responsible for tool use in healthy young adults as well as age-related changes in elderly adults is of main interest. A link to the neuroanatomical correlates of apraxia and tool use impairments is addressed additionally. As presented in this introduction, a variety of studies have focused on different aspects of tool use, age-related changes in simple motor tasks or on the neural basis of apraxia with the help of lesion analyses, but several research questions are still not fully addressed.

The neural basis of planning and executing actual tool use with real objects is not yet fully understood. Based on the literature, it is expected that the knowledge about an object, the type of manipulation and the hand used should influence the neural network of real actions. Furthermore, the organization of the action-related dorsal stream into two processing pathways has so far been hypothesized but not shown in real object-manipulating actions. Considering studies and research on age-related neural changes during actions in elderly adults, it is clear that an investigation of possible alterations of the tool use and action network is currently missing. For the characterization of the tool use network based on lesion analyses of patients with apraxia, it is necessary to consider neural changes in the related brain areas in an age matched group of healthy individuals. This creates a much-needed link between both lines of research. Such comparisons, including neural and behavioral observations in patients with tool use impairments and neural correlates of object manipulations in healthy adults, contributes to a fuller understanding of the neural basis of tool use.

Considering the current gaps in research and possibilities for a more complete overview of the neural basis of tool use, this thesis focuses on the following research goals:

A. The first goal is to analyze the neural correlates of tool use in healthy young adults with the help of fMRI including real objects and actions. A new experimental set up allowing real object manipulations during the measurement is developed to achieve this goal. Of most interest are the effect of the object type, the type of object manipulation and the influence of the hand used on the neural network responsible for actions. Additionally, the structure of the network with respect to its lateralization and separation of functionally specialized processing streams is focused on.

B. The second goal is the evaluation of age-related changes in the brain network responsible for processing tool use actions. The main focus is the comparison between behavioral and neural findings of young and elderly adults and the characterization of altered brain processes in the elderly.

C. Finally, a literature review covers the comparison of findings from fMRI studies and lesion analyses of patients suffering from apraxia. Of main importance are three aspects often impaired in patients: The conceptual understanding of tool use, the spatio-temporal monitoring of tool manipulations, and the sequencing of multi-step activities of daily living (ADL). The review provides a link between the fMRI analyses in healthy adults and clinical observations and extends the view on the neural correlates of tool use.

Taking all these points together, this thesis provides an enhanced insight into the neural correlates of real human tool use in different stages of life and offers a connection to clinical observations to gain a better understanding of brain processes underlying an elemental aspect of our daily lives, as well as neuroanatomical principles of apraxia.

2 The Neural Correlates of Planning and Executing Actual Tool Use

Planning and executing real tool use actions recruits a left-lateralized network which can be subdivided based on the type of action and the object used.

This chapter includes the fMRI study with healthy young participants with the title „The neural correlates of planning and executing actual tool use“. It was published in the Journal of Neuroscience in 2014 by Marie-Luise Brandi, Afra Wohlschläger, Chrisitan Sorg and Joachim Hermsdörfer. This article presents a new method to measure the neural underpinnings of real object manipulations and tool use in an event related design with the help of the "Tool-Carousel". Different experimental factors were analyzed which prove to have an influence on the neural tool use network during real action planning and execution.

Contributions:

The author of this thesis is the first author of the manuscript. M.L.B., A.W., C.S. and J.H. designed research; M.L.B. performed research; M.L.B. and A.W. analyzed research; M.L.B., A.W., C.S. and J.H. wrote the paper.

Behavioral/Cognitive

The Neural Correlates of Planning and Executing Actual Tool Use

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Human tool use is complex, and underlying neural mechanisms seem to be widely distributed across several brain systems; however, neuroimaging studies of actual tool use are rare because of experimental challenges hindering detailed analysis within one acting subject. We developed a "Tool-Carousel" that enabled us to test actual manipulation of different objects during fMRI and investigate the planning and execution of goal-directed actions. Particularly, we focused on the effects of three factors on object manipulations: the type of object manipulated, the type of manipulation, and the hand to be used. The main focus lay on the question of how complex object use compared with unspecific actions are processed and especially how such representations interact with the knowledge about the object in the action-related dorsal stream. We found that object manipulations with both right and left hand recruit a common network strongly lateralized to the left hemisphere especially during planning but also action execution. Specifically, while activity in the ventral stream was involved in processing semantic information and object properties, a dorso-dorsal pathway (i.e., superior occipital gyrus, superior parietal lobule, and dorsal premotor area) was relevant for monitoring the online control of objects and also a ventro-dorsal pathway (i.e., middle occipital gyrus, inferior parietal lobule, and ventral premotor area) was specifically involved in processing known object manipulations, such as tool use. Data further indicate an interaction of ventral stream areas, such as middle temporal gyrus and lateral occipital complex, with both dorsal pathways. These results provide evidence for left-lateralized occipito-temporo-parieto-frontal network of everyday tool use, which may help to characterize specific deficits in patients suffering from apraxia.

Key words: action execution; action planning; fMRI; tool use

Introduction

Using a tool is a natural action we as humans know by heart from our everyday life to interact with our environment. Studies have focused on viewing, recognizing (Beauchamp et al., 2002; Johnson-Frey et al., 2003; Vingerhoets, 2008), imagining (Grèzes et al., 2003; Boronat et al., 2005; Vingerhoets et al., 2009; Wadsworth and Kana, 2011; van Elk et al., 2012), and pantomime tool use (Moll et al., 2000; Johnson-Frey et al., 2005; Hermsdörfer et al., 2007; Króliczak and Frey, 2009; Vingerhoets et al., 2011). Because of the variety of tasks, the neural activation patterns vary, but several brain areas show consistency. The middle temporal gyrus (MTG) for coding semantic information, the supramarginal gyrus (SMG), the anterior intraparietal area (AIP), and superior parietal lobule (SPL) for processing tool use knowledge for grasping and manipulating tools plus the ventral and dorsal premotor areas (PMv, PMd) for executing motor plans, seem to be core regions for conducting actions with objects and tools (for review, see Lewis, 2006). To understand the neural principles of tool use, we think it is necessary to analyze object manipulation as realistically as possible. A few studies have analyzed actual tool use but did not include visual feedback (Hermsdörfer et al., 2007) or were restricted to only a small selection of tools not reflecting the variety of tools known from daily life with familiar size and corresponding object (Inoue et al., 2001; Imazu et al., 2007; Valyear et al., 2012; Gallivan et al., 2013a). Prior knowledge about the manipulated objects (Vingerhoets, 2008), the task (Valyear et al., 2012; Gallivan et al., 2013a), and which hand is used to perform the action (Hermsdörfer et al., 2007; Króliczak and Frey, 2009) seems to influence the mentioned neural network, but how exactly the network is affected by these three factors during planning and executing real actions with objects and especially real tools is yet not fully understood.

To address this gap, the main goal of this study was to analyze the action network under utmost realistic conditions, by investigating planning and executing actual object manipulation. Three factors influencing the network recruited for processing goal directed actions were addressed: the type of object being manipulated, the type of manipulation performed on the object, and the hand used. First, we aimed to define the neural network that is more relevant for planning and executing actions with tools com-

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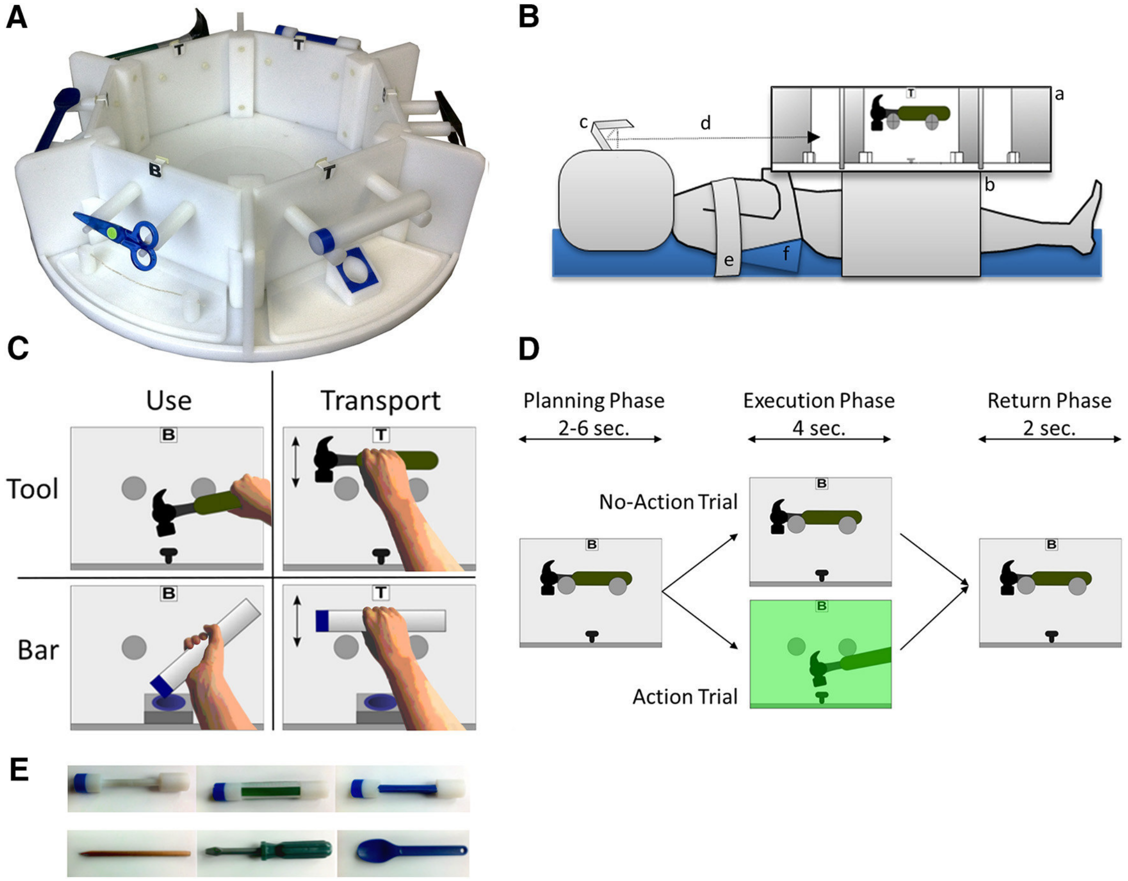

Figure 1. ***A***, The "Tool-Carousel" with six compartments and mountings to hold the tools. ***B***, The experimental setup: ***a***, "Tool-Carousel"; ***b***, adjustable table; ***c***, two-mirror system attached to the head coil; ***d***, visual path to field of vision; ***e***, shoulder belt; ***f***, arm rest. ***C***, Illustration of the four experimental conditions: tool use, tool transport, bar use, and bar transport. All four conditions are performed with the right hand in one and with the left hand in the other run. ***D***, Time course of a trial. Each trial consists of a planning phase (2–6 s long), an execution phase (4 s long), and a return phase (2 s long). In no-action trials, no green light appears; and in action trials, a green light triggers the start of the action. The return phase started when the green light was turned off. No-action trials were used to analyze the planning phase and action trials for the execution phase. ***E***, An exemplary selection of the used stimuli in the experiment; shown are the pen, screwdriver, and spoon and the matched bars.

pared with neutral objects. Second, the neural correlates for the online control of complex functional actions with objects compared with nonfunctional actions were of interest. A special focus laid on the neural underpinnings selective for known tool use. Third, we looked at the structure of the action network while using the dominant compared with nondominant hand and also described the networks with respect to its laterality. The application of a so-called "Tool-Carousel" made it possible to present a variety of actual objects with spatial and temporal precision in the MRI scanner and measure functional images while participants performed real actions.

Materials and Methods

Participants. Twenty healthy participants (9 males) participated in the fMRI experiment. Three had to be excluded (1 male and 2 female) from further statistical analysis because of strong head movements (head motions exceeded 3 mm in translation and 3° in rotation). The group of participants who were included in the analyses had a mean age of 25 years (age range, 21–28 years). All had normal or corrected-to-normal vision, no history of neurological or psychiatric disorders, and were right-handed, as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the local ethics committee.

Experimental setup and design. To present the experimental stimuli, a so-called "Tool-Carousel" (Fig. 1*A*) was installed above the hips of the participants while lying in the MRI scanner. This setup is comparable with the "Grasparatus" from Culham et al. (2003), a device for fMRI experiments, which makes it possible to present real reachable and graspable objects in the MRI scanner.

The "Tool-Carousel" had a diameter of 65 cm and six compartments, which could hold exchangeable mountings for a variety of objects and could be turned around its central axis. It was placed on a table with adjustable height. It was ensured that all participants lay comfortably and could easily reach for the stimuli in the compartments with both right and left hand. The upper arms of the participants were placed on cushions and fixated with a belt to allow easy access to the "Tool-Carousel" while preventing movements of the upper arm and shoulder. The heads of the participants were fixated in the MRI coil with a special set of pads minimizing head motion. A two-mirror system was placed on top of the head coil, which enabled the participants to see the "Tool-Carousel" and their hands (Fig. 1*B*). The mirror system provided a clear image of the whole compartment with the object. Each compartment of the "Tool-Carousel" was separated by a partition, so only one compartment at a time could be seen by the participant. A mirror system was used to view the workspace because tilting the coil and providing a direct view on the "Tool-Carousel" was not possible in our experimental setup. Additionally, keeping a tilted head position for the whole experiment (i.e., ~90 min) seemed to be very uncomfortable for the participants. We consider any bias on the resulting task comparisons due to the visual transformations negligible because all conditions included these transformations and any constant effects should be canceled out.

In general, the experiment comprised three different experimental manipulations with two possible variations each. The first two included the object type and the type of action done with the object. The resulting experimental conditions were randomized on a trial-by-trial basis within subject. The hand used to do the tasks was the third experimental manipulation and did not vary within both of the two runs the participants had to perform. The order regarding which hand was the first to be used during the experiment was randomized across participants. A more detailed description of the different experimental conditions is presented in the following paragraphs.

Two different categories of stimuli were presented during the experiment: tools and neutral objects. The tool set comprised 10 different tools regularly used in daily life (hammer, pen, tweezers, scissor, knife, spoon, screwdriver, key, lighter and bottle opener). The other set of stimuli included 10 differently colored and shaped neutral objects. The neutral objects were mainly bar-shaped; for simplicity, we hereinafter call the neutral objects "bars." To reduce visual and tactile differences between the two stimuli sets, the bars were designed to match the different tools from the first stimulus set as much as possible. The handle of the bars had different shapes (e.g., a small diameter matching the pen or a flat shape matching the nonfunctional part of the spoon and knife). Additionally, the handles of the bars were colored to match the tools. Figure 1*E* shows examples of three tools and the matched neutral bar-shaped object. One side of each bar was marked in blue. All tools had matching mountings to hold the tool and a tool-specific recipient (nail for the hammer, paper for the pen, cotton ball for the tweezers, string for the scissor to cut, piece of bread for the knife, cup for the spoon, rotatable screw for the screwdriver, keyhole for the key, candle for the lighter, and a bottle with crown seal for the bottle opener). All tools were fully functional with respect to the manipulation (e.g., the screw was placed in a winding and could be turned by the screwdriver, the key fit in the keyhole and was rotatable). Goal attainment was functional in some but not in all actions (e.g., the pen left a trace on the sheet of paper, but the nail did not move into the material during hammering and the lighter did not produce a flame due to security reasons). Therefore, our study addresses the neural correlates of actual tool manipulation but does not intend to reflect representations of goal attainment. In case of the bars, a blue marked opening was placed at the bottom of the mounting, in which the blue end of the bar was to be inserted. All components of the "Tool-Carousel," as well as all objects, were made of plastics. fMRI compatibility was verified in test scans.

The task was to either use the different objects or to transport them, the latter meaning to grab and lift the object and return it to the mounting. The participants had to perform two runs of functional MRI: one in which they had to use the dominant right hand and the other in which they had to use the nondominant left hand. The order in which the hands were tested was randomized across subjects. In case of the tools, the action typical for the tool should be performed by the participant (e.g., hit the nail with the hammer, write with the pen on paper). To be used comfortably, each of the tools required a different tool-specific functional grip and movement (e.g., grasping the hammer at the handle and move it up and down to hit the nail). The tools were placed in a way that the action could be performed promptly without additional adjustments of the grip (the handle of the tool was placed to the right while the participants used the right hand and left while they used the left hand, respectively). To use the bars, the participants had to put the blue marked end of the bar into the blue opening on the bottom of the mounting (Fig. 1*C*). Dependent on the placement of the marked end in the mounting (medial or lateral) and the hand used, the participants had to grasp the bar with an overhand (pronated) or underhand grip (supinated) to place the blue end into the opening comfortably (Rosenbaum and Jorgensen, 1992; Marangon et al., 2011). In half of the trials the marked end of the bar was placed to the left, the other half to the right. Therefore, as for the tools, the grip to comfortably use the bar had to be adjusted according to the demands of the task. The order of orientation was randomized across the experiment. A small sign at the top of the mounting showing either the letters "B" (for "benutzen," the German word for "use") or "T" ("transportieren" for "transport") indicated which task the participants had to perform. This setup resulted in four different main conditions: (1) tool use, a functional grip and movement of a known object; (2) tool transport, a nonfunctional grip and movement of a known object; (3) bar use, a functional grip and movement of a neutral object; and (4) bar transport, a nonfunctional grip, and movement of a neutral object.

The experiment had a rapid event-related design with 200 trials per run. Each of the four conditions was comprised of 40 trials (four repetitions for each tool or each bar), resulting in 160 condition trials and 40 control trials. During the control trials, an empty compartment of the tool carousel was shown, these trials served as a control condition for the comparison in the statistical analysis. To ensure an optimal trial order, the Genetic Algorithm toolbox (Wager and Nichols, 2003) for event-related designs was used to create a randomized trial order for each run. The order of objects was randomized across subjects.

Each trial consisted of a planning phase with a duration of 2–6 s in which the object and the cue for the action was presented, followed by an execution phase in which a green light triggered the start and the duration of the cued action. When light was turned off after 4 s, the participants had to stop the action and to return the object to the mounting in maximum 2 s time (return phase) (Fig. 1*D*). During the intertrial interval (varying equally between 1 and 2 s), the "Tool-Carousel" was turned to present the next stimulus. In half of the trials of each condition, no green light appeared, resulting in 80 action and 80 no-action trials. The order of trials with and without the green light and also the time of the onset of the green light (2–6 s) varied randomly across the run, making it impossible for the participants to predict, if a trial is an action or no-action trial.

Procedure. Before the fMRI measurement, all participants had to answer a questionnaire, checking their knowledge about the objects used in the experiment and how familiar they are with the usage. Here the participants had to name the object, state if they know the function of the object (scale ranging from 0 = not at all to 3 = yes, very well), how to use it (scale ranging from 0 = not at all to 3 = yes, very well), how often they have used it (scale ranging from 0 = never to 3 = often), how regularly they use it (scale ranging from 0 = never to 4 = daily), how often they have to use it during their job or studies (scale ranging from 0 = never to 4 = very often), if it is an essential object for their daily life (0 = not at all to 2 = very much) and if they own the object.

Experimental procedures and tasks were explained to the subjects via a video instruction on how the different objects are thought to be used and transported followed by a training of all tasks while already laying comfortably in the scanner. The position of the "Tool-Carousel" was adjusted according to the participants' individual size and arm length to ensure that all objects could be used comfortably and according to the instructions. No instance was observed when an object could not be properly grasped or used due to the mounting of the object acting as an obstacle. Participants were asked to do the actions at least once and perform the task carefully without rushing, to avoid short and quick movements, which could disturb data acquisition. The manipulation of all experimental conditions was trained with all objects until participants were able to perform all tasks accurately with both left and right hand in the given time of the execution phase. During the fMRI measurement, Presentation Software (Neurobehavioral Systems) was used to give acoustic instructions via headphones on timing of trials to an operator within the scanner room. The operator exchanged task cues and objects for each trial and turned the "Tool-Carousel" on the acoustic cueing. The subjects received no acoustic simulation. A camera placed at one end of the MRI scanner recorded the hand movements and workspace of the participants.

Video analysis. The recordings of the camera were used to rate the participants' performance and to evaluate the accuracy of the onset of trials and the duration of hand movements. For the performance rating, the number of errors was counted per participant. One type of error included general task errors and was rated with the scale 0–1: a score of 1 meaning the task was performed according to the cue. For the use conditions, the grip and movement errors were counted. Grasping errors were also rated with the scale 0–1: a score of 1 was given if a functional grip was used to manipulate the object. In case of the tools, the object had to be held on the nonfunctional end with a hand position, enabling the participant to manipulate the tool as usual (e.g., grasp the handle of the hammer or hold the pen in the learned writing position). The correct grip was shown to the participants in the introduction video before the testing. If a subject held the tool in an uncommon way not according to the instructions, the trial was scored with a 0. In the condition bar use, a functional grip was achieved if the participants discriminated between an overhand or underhand grip dependent on whether the blue marked end of the bar was on the medial or lateral side (Rosenbaum and Jorgensen, 1992; Marangon et al., 2011). Another scored aspect of the task was the correct movement performed with the object (scale 0–1). If the subjects moved the object according to its function and how it was shown to them in the instruction, the trial was scored with 1. On the other hand, if the movement was not executed correctly or incomplete (e.g., only moving a tool to the target without the function specific movement or not placing the marked end of the bar in the opening), the trial was scored with 0. Additional to the use condition, also the transport condition was rated. This condition was performed correctly if the object was grasped, lifted, and returned as instructed before the experiment. It was evaluated if a functional grip (as in the use condition) or a nonfunctional transport grip was used. The latter was shown in the introduction video and included grasping the tool in the middle to lift it, but no further tool-specific grip adjustment. In the end, the observations of both runs were averaged for all subjects for each error category.

Even though the participants were asked to perform the movement during the execution phase while the green light was on and return the object when the light was turned off, it cannot be guaranteed that the durations of the hand movements are exactly the same in all trials and participants across the experiment. Therefore, next to the general task performance, also the timing of each individual participant was determined in a video analysis. A motion detection analysis was done with a MATLAB (Release 2012a, MathWorks) based script. One search area and one reference area were selected in each video. The search field included the pixels covering the workspace and hands of the participant, and the reference field included a part of the bore of the MRI scanner where no hand or any other movement occurred. The videos were converted to single picture frames (12.5 frames per second); and to detect motion, the pixels of the search and reference fields of one picture frame were subtracted from the pixels from the following picture frame. The mean across all pixels of these differences was saved as a vector representing a time course of changes in the search and reference field, respectively, for each subject. A movement was detected if the value exceeded a certain threshold. This threshold was calculated for each subject individually and represented a mean value of a time period of 4 s from the beginning of each run in which no hand movement occurred. The results from the motion detection from the reference field only show peaks when the action signal (green light) was turned on and off. This information was used to confirm that the detected hand movements in the search field were related to the task and represent the action in the execution phase. Correct performance of the automatized motion detection was verified by visual inspection. In general, subjects' movements filled the 4 s execution time in all conditions. Quantitative analysis revealed that the mean time across subjects needed for the tool condition was 4.2 s, for bar 4.0 s, for use 4.4 s and for transport 3.8 s. These results led to a significant ($p < 0.05$, Bonferroni corrected for two comparisons) difference in duration of 0.2 s for the comparison of objects and 0.6 s for the comparison of the task. The periods of each subject's hand movements were introduced into the first-level analysis to ensure an accurate modeling of events and to control for the variance in duration across conditions (this process is explained in more detail in fMRI analysis).

MRI measurement. All fMRI measurements were performed on a Siemens 3 Tesla Verio MRI scanner. T1-weighted anatomical images were acquired with the MP-RAGE sequence, whereas the BOLD echo-planar images were measured using a T2*-weighted gradient echo sequence with the repetition time TR = 2000 ms, echo time TE = 30 ms, field of view = 192 mm, flip angle $\alpha = 90°$, matrix = 64 × 64, slices = 35, slice thickness = 3 mm and voxel size = 3 mm × 3 mm × 3 mm.

fMRI data analysis. The entire data analysis was performed with SPM8 (Statistical Parametric Mapping software; Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk). Before entering the statistical analysis, the fMRI data were preprocessed by using a slice time correction, realigning the images to correct for movement artifacts, coregistering the anatomical, and normalizing all images to standard space (Montreal Neurological Institute, see SPM software). Thereafter, the functional datasets were smoothed with a Gaussian kernel of 8 mm for group analysis.

The statistical analysis was performed at two levels. At the first level for each subject, the onsets of each condition were modeled in a GLM as events, which are represented as stick functions and convolved with the hemodynamic response function. The design matrix comprised two sessions, representing the runs in which the subjects used the right or the left hand, respectively. The design matrix for one run was composed of 15 regressors representing the experimental conditions and six regressors comprising the realignment parameters. The 15 condition regressors included a separate regressor for the planning phases of each condition for the no-action trials as well as the action trials (two times: tool use, tool transport, bar use, bar transport). Four additional regressors modeled the execution phase of the action trials of all conditions as events. The 13th regressor represents the control condition. The 14th modeled the individual trials in which the subjects made errors. The last regressor included the duration of hand movement, which was detected for each subject individually by the motion detection analysis of the video recording. This regressor, therefore, covers the hand movement during the execution phase and return phase of all conditions in one. Because this study does not aim to analyze the basic sensorimotor processing of movements, the purpose of this regressor is to explain the variance in the data, which is caused by the duration of hand movements the subjects need to perform the different tasks and to return the objects. To verify that this regressor explains mainly basic sensorimotor processes as during the period of hand movement, a second-level one-sample *t* test of this regressor was performed.

At the second level for the main activation analysis, contrast images of each participant were entered into a 2 × 2 × 2 factorial design with the factors object (level: tool or bar), task (level: use or transport), and hand (level: right or left). Separate second-level analyses were performed for the main effects and interactions of the planning and execution phase, respectively. The contrast images which entered the factorial design included the comparisons of each condition separately to the control condition. The second-level analysis of the planning phase comprised the contrast images of the no-action trials only, which eliminates the influence of actual movement in this data analysis. The analysis for the execution phase includes the contrast images of the action trials only. A brain mask was created for action planning and execution and applied to the second-level analysis, including the added activations of all conditions compared with the control condition at a threshold of $p < 0.001$. The anatomical labeling of the results was done with the Anatomy Toolbox (Eickhoff et al., 2005) and the graphical display of the statistical maps with the BrainNet Toolbox (Xia et al., 2013). Bar plots showing the contrast estimates of peak activations of clusters at a threshold of $p < 0.05$ (and family-wise error [FWE] correction) were constructed to display activations toward the control condition for all four conditions separately.

Laterality index (LI). To evaluate the laterality of the tool use and action network the LI was calculated with the LI toolbox (Wilke and Lidzba, 2007) for each condition and each subject on a first-level basis to test the laterality across the group. Additionally, the LIs of the activation maps of the second-level analysis were estimated. Because the LI is strongly dependent on the threshold used for the images in the analysis, the bootstrap method was used as recommended by the developers of the toolbox (Wilke and Schmithorst, 2006; Seghier, 2008). The bootstrap method creates 10,000 LIs, which are calculated at a range of different thresholds. Taking the results from the different thresholds into account, a weighted LI is calculated. These values range from −1 (right sided lateralization) to 1 (left-sided lateralization). To analyze the laterality of the network in more detail and ensure that the calculated LIs are not biased by contralateral motor-sensory processing, the calculation for the individual images was performed for the occipital, temporal, parietal, and frontal lobe, whereas the primary sensorimotor cortices were excluded and analyzed separately.

To test for significant difference of LI from zero (zero corresponds to symmetrical activation), a *t* test of the subjects' LIs was performed for each condition separately. Additionally, the individual LIs were entered into a three-way ANOVA with the three factors object, task, and hand to evaluate significant main effects for each factor.

Results

Behavioral data: questionnaire

The questionnaire, which was filled out by the participants before the start of the experiment aimed at measuring if the participants knew the objects used in the experiment and how familiar they are with using them. The median score of the questions testing for tool knowledge (naming the tool, knowing function, and how to use it) was 70 points (range, 66–70 points). The possible maximum score was 70 points, showing that all participants knew all tools (one scored only 66 because this participant did not clearly recognize one object on the given photo but knew it after clarification). Regarding the bars, the median score was 0 (range, 0–3 points), showing that participants, as expected, had no prior knowledge of the bar's function or use. Concerning the familiarity of objects, the participants scored a median of 75 points (range, 54–98 points) for the tools and 0 for the bars. The possible maximum score was 130 points per participant, which would mean that all included tools had to be used on a daily basis during the participants job and daily routine. The minimum score was 0, which would indicate that the object has never been used by the participant before and its usage is not familiar to him or her. All participants owned all of the tools but not the bars, except for two participants, who did not own a lighter. All in all, the results of the questionnaire show that all participants knew the tools and were familiar with using them but did not do so for the bars.

Behavioral data: video analysis

Performance of the participants was evaluated by scoring the video recordings of their hands and the workspace. This evaluation was performed to ensure correct performance according to the cues and instructions and to assess whether functional grips and movements were used. For all conditions, it was evaluated whether the correct action according to the cued experimental condition was performed. In total, the median number of errors was one error (range, 0–2 errors) per participant (during a total of 400 trials). In the following, only trials in which the correct cued task was performed will be considered. During the tool use condition, the median error score regarding the use of a functional grip was 1 (range, 0–5 errors), and for mistakes concerning the movement of the tool was 0 (range, 0–4 errors). There was no significant difference of the number of mistakes made between the two runs. In all trials of the condition tool transport, a nonfunctional grip was used to transport the tool by all participants. The condition bar use was performed correctly by all participants in all trials. The participants made an overhand grip in all possible 20 trials, which required this type of grip. In the 20 trials in which an underhand grip was appropriate, the median number of underhand grips was 19 (range, 20–13). In the remaining trials, an overhand grip was used. This shows subjects adjusted the grip dependent on the objects properties (is the marked end on the medial or lateral side). The participants made no movement errors in the bar use condition. In the bar transport condition, the same lifting grip was used as in the tool transport condition in all trials.

All in all, the behavioral results showed that the task was mostly performed correctly and that the condition tool use and bar use were performed using a functional grip and movement for each object relative to the goal of the action. On the other hand, during both the condition tool transport and bar transport, a nonfunctional transport grip and movement was used.

Table 1. Anatomical locations and the *p* values of peak voxels of the one-sample *t* test results for the subjects' individual period of hand movements[a]

Brain area	*p*
Left hemisphere	
Precentral gyrus	0.0381
Superior parietal lobule, SPL 5A	0.0010
Inferior occipital gyrus	0.0090
Postcentral gyrus	0.0005
Right hemisphere	
Inferior frontal gyrus (*pars opercularis*)	0.0001
Inferior frontal gyrus (*pars triangularis*)	0.0010
Middle frontal gyrus	0.0031
Superior frontal gyrus	0.0008
Superior medial gyrus	0.0450
Insula	0.0037
Lingual gyrus	0.0071
Postcentral gyrus	0.0000
Precuneus	0.0000
Supramarginal gyrus	0.0000
Inferior temporal gyrus	0.0042
Superior temporal gyrus	0.0000

[a] Data are the *p* values of the peak voxel of a cluster in an anatomical area. Only clusters are reported, which survive a threshold of $p < 0.05$ (FWE).

Movement duration

To clarify which brain regions are sensitive to possible variations of the movement duration, a second-level analysis was performed. The anatomical location of the peak voxels and the corresponding *p* values are given in Table 1. Results are shown with a threshold of $p < 0.05$ and an FWE correction. The results of this analysis revealed mainly the sensorimotor cortices of both hemispheres and an occipito-temporo-parieto-frontal network of right, but none of the left, side brain areas involved in tool use as reported below.

fMRI activation analysis

The following section reports the neural responses for the manipulation of tools and neutral objects during action planning and execution and the main effects of the factors object, task, and hand. As a first step, activation caused by all task conditions versus the control condition during action planning was calculated to determine the brain areas necessary for processing the planning of object related manipulations independent of specific functions and object semantics. The activity maps are shown at a threshold of $p < 0.05$ with an FWE correction. This analysis showed a left-sided network (Fig. 2*A*, top), including clusters in the temporal lobe, such as the fusiform gyrus (FG) and lateral occipital complex (LOC), MTG, clusters in the parietal lobe (SPL, SMG), including anterior and posterior parts of the intraparietal area, frontal activation, including PMv, PMd, insula lobule, and a cluster in the middle frontal gyrus (MFG). The LI for this contrast is 0.64 for frontal, 0.92 for parietal, 0.69 for temporal, and 0.58 for the occipital lobe, whereas the LI for the sensorimotor cortex is 0.99. The same analysis was performed for the execution phase (Fig. 2*A*, bottom) showing a wider bilateral network with additional activations in primary sensory and motor cortex in both hemispheres. The calculated LI for this contrast is 0.45 for frontal, 0.34 for parietal, 0.06 for temporal, and −0.091 for the occipital lobe, whereas the LI for the sensorimotor cortex is 0.58.

The tool network during actual action planning and execution

To statistically determine the brain regions that are more active for planning actions with known objects (tools) compared with neutral objects (bars), the contrast tool versus bar was calculated

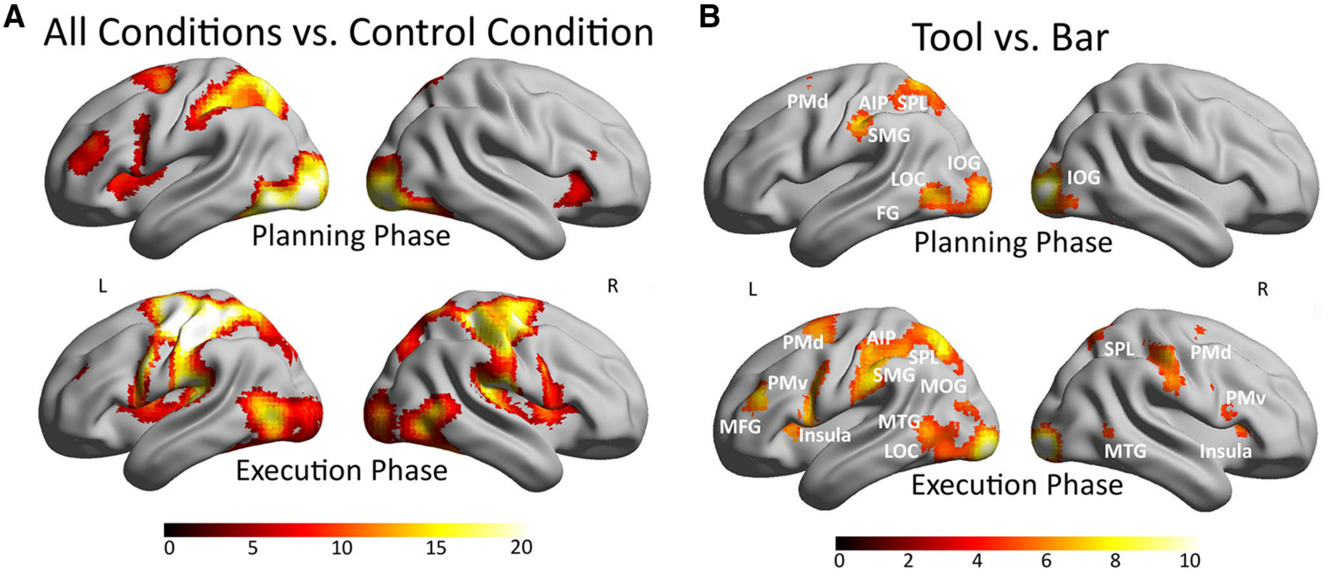

Figure 2. Whole-brain results for the action network in ***A*** and the main contrast for the factor object in ***B***. ***A***, The activity maps of the contrast all conditions versus control condition shown for the planning phase in the top and for the execution phase on the bottom. ***B***, The activity map of the contrast tool versus bar is shown for the planning phase in the top and for the execution phase in the bottom. All results of Figure 2 are shown at a threshold of $p < 0.05$ (FWE corrected) on a rendered brain. The color scale under the brain images indicates the range of the T values from low values in dark red to high values in white. IOG, Inferior occipital gyrus; MOG, middle occipital gyrus.

and is shown in Figure 2*B* (top) at $p < 0.05$ (FWE corrected). The results showed an overall mainly left-sided activation pattern (LI frontal lobe, 0.75; LI parietal lobe, 0.83; LI temporal lobe, 0.49; LI occipital lobe, −0.38; LI sensorimotor cortex, 0.84). Additional to clusters in inferior occipital gyrus, the LOC, MTG, and FG were activated. In the parietal cortex, the SPL, SMG, and the inferior parietal lobe, including the AIP, showed a specification for the tool conditions compared with bars. A frontal cluster was located in the PMd and is listed in Table 2 with the other results. No specific region was activated for the opposite contrast bars versus tools during action planning.

The execution phase was analyzed in the same way (Fig. 2*B*, bottom). The contrast tool versus bar revealed activation differences in the same temporal, parietal, and frontal regions as during the planning phase, but to a larger extent and with additional clusters in the PMv, PMd, insula, MFG, primary sensory, and motor cortex. The network is still lateralized to the left, although to a lesser extent due to the recruitment of the right-sided areas while executing actions with the left hand. Because the condition bar also required hand movements, contrast differences in primary motor activation were however not significant. The anatomical locations of the clusters and the statistical values of the peak voxel in all clusters of both contrasts can be found in Table 2. The reverse contrast bar versus tool for execution phase did not show significant clusters surviving at this threshold.

Neural correlates of using objects and the knowledge of how to use a tool

To study the influence of the manipulation type on the action network, we focused on the factor task in this part of the analysis. To define the brain regions engaged in functional tool use and object manipulation independent of the specific object type, the contrast use versus transport was calculated. This analysis was performed for both planning phase and execution phase. For the planning phase, two clusters were found only at a threshold of $p < 0.001$ (uncorrected). One was located in left SPL and the other in the left PMd. The uncorrected activation map of the planning phase is shown in blue as an overlay on the activation map of the execution phase in Figure 3*A*. The corresponding uncorrected p values of the peak voxels are listed in Table 2. The activation map of the execution phase is shown at $p < 0.05$ with an FWE correction (red color scale). The network involved in controlling a functional grip and the manipulation of an object included the left LOC, a cluster in the left lateral part of the superior occipital gyrus (SOG) close to the parietal-occipital sulcus, SPL, and left PMd, the latter two matched the areas also described for the planning phase. Additionally, primary sensory and motor cortices were more active during the use than during the transport of an object. This network for functional use, including the grip and specific movements, was mainly lateralized to the left hemisphere, except for a cluster in the right SPL resulting in the following LIs: LI frontal lobe, 0.76; LI parietal lobe, 0.76; LI temporal lobe, 0.81; LI occipital lobe, 0.85; LI sensorimotor cortex, 0.68. The contrast estimates and 90% CI of each of the four experimental conditions versus control condition were plotted for regions of interest (Fig. 3*A*). Compared with the control condition, all regions were activated in all separate task conditions, but the responses were higher for the condition use compared with transport independent of which object was used. However, the use of tools in all regions produced a higher response than the condition bar use.

To define the brain regions coding function-specific tool knowledge during execution, the interaction between the factors object and task was calculated ((tool use − tool transport) vs (bar use − bar transport)). To restrict the analysis to regions with the highest sensitivity to tool use, but not to the other three conditions, the interaction was masked with the intersection of the three contrasts: tool use versus tool transport, tool use versus bar use, and tool use versus bar transport (threshold for the masking contrasts was $p < 0.001$ uncorrected). These regions therefore showed the highest sensitivity for the use of tools compared with goal-directed manipulation of neutral objects and do not reveal object-specific activations for nonfunctional transport actions. The other three conditions (tool transport, bar use, and bar trans-

Table 2. Anatomical locations and the *p* values of peak voxels for all calculated contrasts[a]

	Planning phase			Execution phase					
Brain area	All versus baseline	Tool versus bar	Use versus transport	All versus baseline	Tool versus bar	Use versus transport	Interaction of task × object	Left versus right	Right versus left
Left hemisphere									
Frontal lobe									
Inferior frontal gyrus, PMv	0.0000			0.0000	0.0000		0.0001		
Inferior frontal gyrus (*pars orbitalis*)					0.0000				
Inferior frontal gyrus (*pars triangularis*)								0.0035	
Middle cingulate cortex	0.0000			0.0000					
Middle frontal gyrus	0.0000			0.0000	0.0000			0.0107	
Precentral gyrus				0.0000			0.0001	0.0065	0.0227
SMA				0.0000	0.0010				
Superior frontal gyrus				0.0000					
Superior frontal gyrus, PMd	0.0000	0.0088	0.0001*			0.0007			
Insula lobe									
Insula	0.0000			0.0000	0.0000				
Occipital lobe									
Cuneus							0.0003		
Inferior occipital gyrus	0.0000	0.0000		0.0000	0.0000				
LOC		0.0000		0.0000	0.0040	0.0017			
Middle occipital gyrus	0.0000	0.0242		0.0000	0.0010		0.0001		
Superior occipital gyrus				0.0000	0.0160	0.0025	0.0003		
Superior occipital lobule		0.0003							
Parietal lobe									
Anterior intraparietal area	0.0000	0.0048						0.0347	
Inferior parietal lobule					0.0000			0.0130	
Inferior temporal gyrus					0.0000				
Postcentral gyrus	0.0000			0.0000		0.0000	0.0141	0.0015	0.0034
Precuneus	0.0000								
Superior parietal lobule	0.0000								
Superior parietal lobule, SPL 7A		0.0000	0.0004*	0.0000	0.0000	0.0370			
Supramarginal gyrus		0.0000			0.0000		0.0025		
Temporal lobe									
Fusiform gyrus	0.0000	0.0006		0.0003	0.0020				
Inferior temporal gyrus				0.0000				0.0178	
Middle temporal gyrus					0.0000	0.0161		0.0131	
Superior temporal gyrus				0.0000				0.0003	
Temporal pole								0.0383	
Right hemisphere									
Frontal lobe									
Inferior frontal gyrus, PMv				0.0000	0.0010				
Inferior frontal gyrus (*pars triangularis*)	0.0000								
Inferior frontal gyrus (*pars orbitalis*)	0.0000								
Middle cingulate cortex				0.0000	0.0000				
Middle frontal gyrus					0.0040				
Precentral gyrus				0.0000				0.0000	
SMA					0.0020				
Insula lobe									
Insula	0.0180			0.0000	0.0010				
Occipital lobe									
Calcarine gyrus				0.0252					
Inferior occipital gyrus	0.0000	0.0000		0.0000	0.0000				
LOC				0.0000					
Parietal lobe									
Postcentral gyrus				0.0000	0.0000				
Precentral gyrus				0.0000					
Precuneus	0.0000			0.0000	0.0000				
Superior parietal lobule	0.0000					0.0015			
Superior parietal lobule, SPL 7A				0.0000					
Temporal lobe									
Fusiform gyrus	0.0000	0.0009		0.0000					
Middle temporal gyrus				0.0000					
Temporal pole					0.0160				

[a] Data are the *p* values of the peak voxel of a cluster in an anatomical area. Mainly clusters are reported, which survive a threshold of $p < 0.05$ (FWE).

*Uncorrected *p* values.

port) were not significantly different from each other. The statistical map is shown in Figure 3*B* at $p < 0.05$ (FWE corrected). In addition to a cluster in the posterior MTG clusters were detected in the middle occipital gyrus close to V5, PMv, in a posterior part of the SMG, and the medial part of the SOG. Additionally, a cluster in the left postcentral gyrus showed an interaction. This network included exclusively left-sided clusters, which are listed in Table 2. The contrast estimate and 90% CI of each of the four

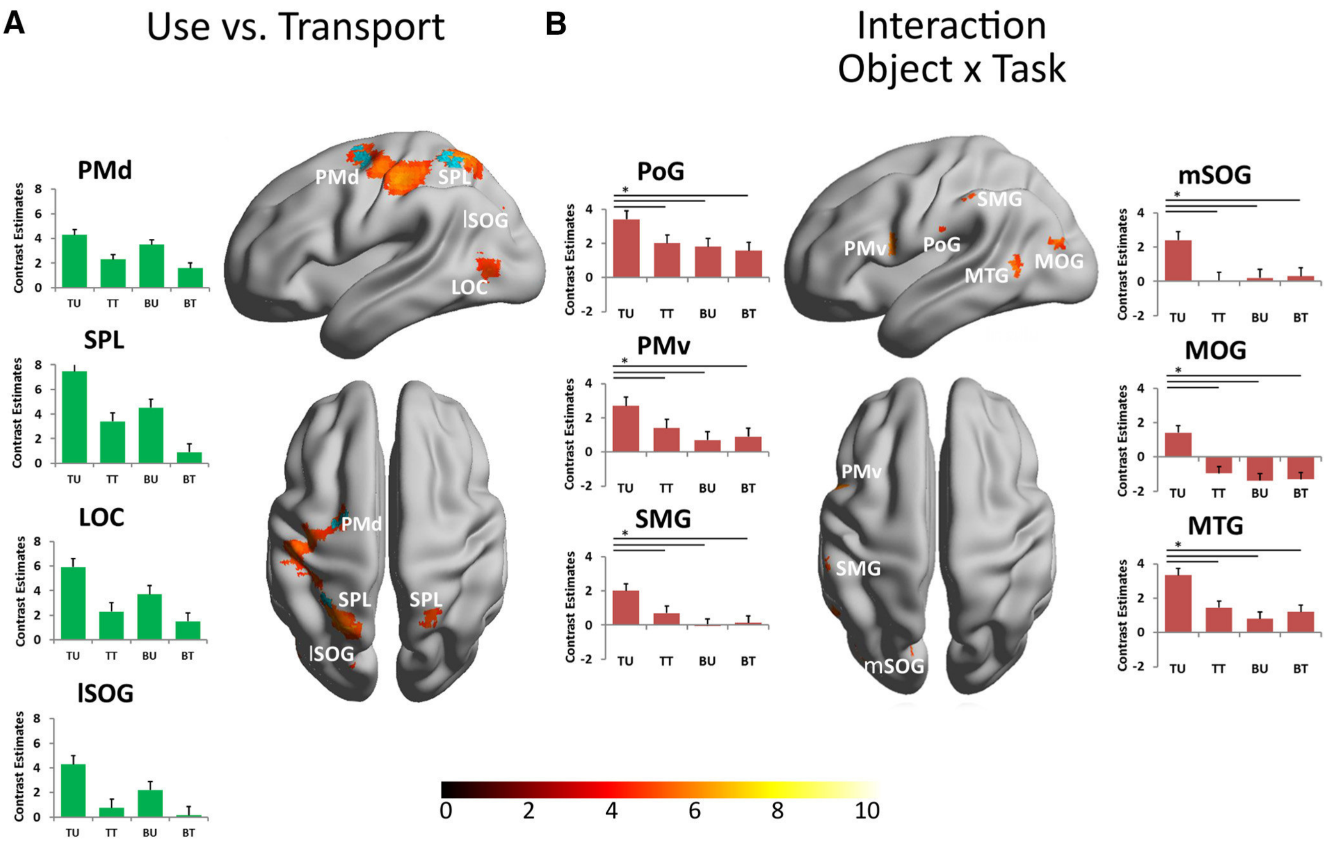

Figure 3. Results showing the influence of the factor task on the action network. ***A***, Activity map of the contrast use versus transport is shown for the execution phase. Bar plots represent the contrast estimates of the peak voxel and 90% CI in the labeled cluster for all four conditions. TU, Tool use; TT, tool transport; BU, bar use; BT, bar transport. The uncorrected activations during the planning phase that did not survive the correction for multiple testing are shown as a blue overlay. ***B***, Activity maps of the interaction between the factor object and task ((tool use vs tool transport) − (bar use vs bar transport)) is superimposed onto a rendered brain for the execution phase. All results of Figure 3 are shown at a threshold of $p < 0.05$ (FWE corrected). *The three lines across the bar plots indicate that the contrast estimates of the condition tool use is significantly higher than in the other conditions with a threshold of $p < 0.001$. The color scale under the brain images indicates the range of the T values from low values in dark red to high values in white. MOG, Middle occipital gyrus; PoG, postcentral gyrus.

experimental conditions versus control condition were plotted for the regions of interest (Fig. 3*B*). The LIs for the interaction are 0.31 for the frontal lobe, 0.65 for the occipital lobe, 0.77 for the parietal lobe, 0.035 for the sensorimotor cortex, and 0.52 for the temporal lobe. The same analysis for the planning phase or any other interaction between the factors object and task revealed no significant clusters surviving a threshold of $p < 0.05$ with an FWE correction.

Handling tools with the dominant and nondominant hand

The results above for the combined data of the right and left hand showed a left-lateralized tool network for action planning and execution independent of the used hand. To compare the structure of the action network for the dominant and the nondominant hand (in our case right and left hand, respectively), the contrasts right versus left and left versus right were calculated. No significant differences were found in the planning phase at a threshold of $p < 0.05$ (FWE corrected) for both contrasts. The direct comparison of both conditions for the execution phase revealed for the contrast right versus left, as could be expected, a cluster in the left motor cortex (Fig. 4). The calculation of the LIs revealed a value of 0.94 for frontal lobe, −0.47 for occipital lobe, 0.18 for parietal lobe, 0.96 for sensorimotor cortex, and 0 for temporal lobe. The reverse contrast (left vs right) revealed a left-sided activation pattern next to a strong cluster in the right motor cortex and SMA; the activations include temporal (superior temporal gyrus, MTG, ITG), inferior parietal (SMG, AIP), and lateral frontal areas (MFG, PMd, PMv). The following LIs were calculated for this contrast: 0.80 for frontal lobe, 0.89 for occipital lobe, 0.93 for parietal lobe, −0.43 for sensorimotor cortex, and 0.95 for temporal lobe.

The interactions between the factors hand and object or task did not reveal significant clusters surviving a threshold of $p < 0.05$ with an FWE correction.

LI

To verify the lateralization of the network relevant for planning and execution actions with tools and neutral objects across subjects, the LI for all lobes and conditions was calculated separately, tested for significance, and compared for the factors object, task, and hand. The mean LI and p value for all conditions and lobes are shown in Table 3 for action planning and execution. The mean LI, p value, and F value of main effects for each factor are shown in Table 4 for the planning phase and execution phase. The results indicate a significant left-sided lateralization during action planning in the parietal lobe, temporal lobe, and sensorimotor cortex in almost all conditions. During action execution, a significant left-sided lateralization is obvious for all use conditions in the frontal lobe and for tool use right and left and bar use left in the parietal lobe. A right-sided lateralization could be found for the right-hand conditions in the temporal lobe. In the sensorimotor cortex, a clear left-sided lateralization can be found in the right-hand condition, whereas the left-hand condition shows a weak right-sided lateralization, which is only significant

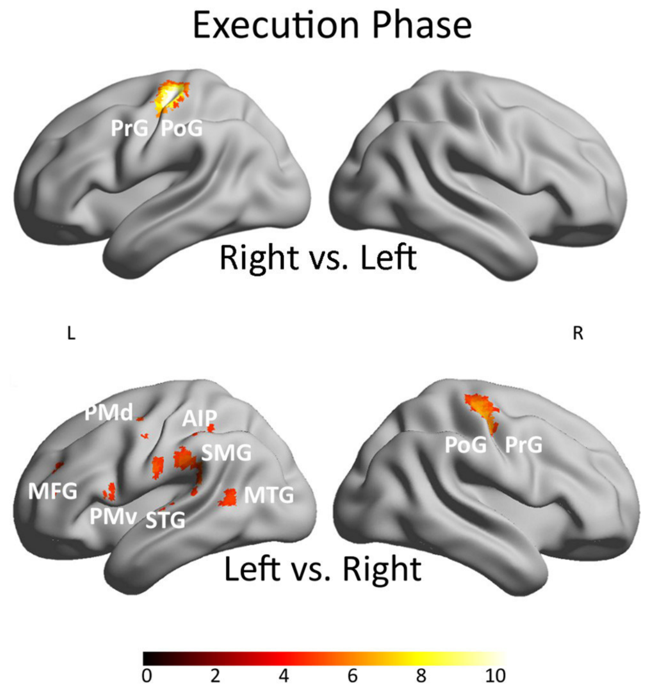

Figure 4. Results showing the influence of the factor hand on the action network. Activation maps of the contrast right hand versus left hand on the top and left hand versus right hand on the bottom for the execution phase. All results of Figure 4 are shown at a threshold of $p < 0.05$ (FWE corrected) on a rendered brain. The color scale under the brain images indicates the range of the T values from low values in dark red to high values in white. IOG, Inferior occipital gyrus; STG, superior temporal gyrus; PrG, precentral gyrus; PoG, postcentral gyrus.

for the condition bar transport left. The comparison of factors show for the planning phase a significant main effect for the factor object with a higher left-sided lateralization for tool than bar in the frontal, parietal, and temporal lobe as well as in the sensorimotor cortex. During action execution, a stronger left-sided lateralization is found in the parietal lobe for the condition tool compared with bar and in all areas for use compared with transport. A significant main effect for the factor hand can be found in the temporal lobe (stronger left-sided lateralization for left than right), occipital lobe (stronger left-sided lateralization for left than right), and the sensorimotor cortex (stronger left-sided lateralization for right than left). In summary, this analysis shows that especially the process of action planning, but also the execution of object use, is left-lateralized.

Discussion

The current study aimed to describe the neural bases of actual tool use by investigating planning and executing actions with known tools and neutral objects for the dominant and nondominant hand. A wide strongly left-lateralized network was identified, including parietal and frontal areas and areas of the ventral stream in addition to the obligatory primary sensorimotor areas as related studies have reported (Inoue et al., 2001; Hermsdörfer et al., 2007; Gallivan et al., 2013a). More specifically, we are able to extend the characterization of three previously reported posterior streams (Milner and Goodale, 2008; Binkofski and Buxbaum, 2013) with distinctive functions in real tool use: the ventral stream that is relevant for processing semantic tool information and object properties, a dorso-dorsal pathway that is relevant for online monitoring the grip and movements of objects during complex actions, and, additionally, a ventro-dorsal pathway that is specifically involved in processing known object manipulations, such as tool use.

Direct evidence for the separation of the dorsal stream in two processing pathways

By looking at complex goal-directed actions irrespective of object identity compared with simpler actions, we are able to define areas that are increasingly recruited for monitoring the online control of demanding object manipulations. The comparison of the condition use and transport showed higher activations in left SPL, PMd, SOG, and LOC. In previous research, Martin et al. (2011) noted that additional to other areas left- and right-handers show activity in SPL, reaching from the posterior parietal sulcus to the parietal-occipital sulcus and in PMd during grip selection and grasp planning. The cluster in the SOG of our results is close to the superior parietal occipital complex, which several studies have described as an important cerebral region in reach-to-grasp actions in humans (Cavina-Pratesi et al., 2010; Gallivan et al., 2011; Monaco et al., 2011). A stronger recruitment of these "grip regions" could be based on the fact that the selection of a functional grip is more demanding and complex than a simpler transport grip (Verhagen et al., 2013). Furthermore, it might not only be the complexity and the intended goal of the performed action, which is specific for each of the two conditions, but also the process of action selection. Because the same action was performed during the transport condition for all trials but a variety of different actions during the use condition, we can assume that the found neuronal circuit might also be involved in the action selection process. Additionally, it is important to say that all stated regions have been mentioned as being part of the dorso-dorsal pathway described by Binkofski and Buxbaum (2013). The dorso-dorsal pathway is running from the visual area V6 to the SPL ending in the PMd (Rizzolatti and Matelli, 2003). It is necessary for monitoring correct reaching and grasping movements to handle an object dependent on the object's properties (Grol et al., 2007). The increased load of online control and necessary movement adjustments during the use condition, irrespective of object type compared with the transport, could be the reason that the pathway along the SOG, SPL, and PMd is recruited stronger (Glover et al., 2005, 2012; Striemer et al., 2011). As our results show, SPL and PMd are not only relevant for the online control of monitoring actions but possibly also for planning demanding actions. Even though the comparison of planning the use and transport of actions did not survive the correction for multiple testing, it is interesting to see that a similar activation pattern can be found for planning and executing complex actions. Interestingly, next to these dorsal stream areas, also the LOC of the ventral stream is sensitive for using known but also neutral objects. Its involvement in object recognition and therefore in tool-related tasks is known (Grill-Spector and Malach, 2004; Vingerhoets, 2008; Wurm et al., 2012). Additionally, it seems to be relevant for processing the dimensions of neutral objects, which are relevant for grasping (Monaco et al., 2014) and also when viewing unfamiliar or infrequently used tools compared with familiar tools (Vingerhoets, 2008). LOC coactivation with the dorso-dorsal stream in the use condition indicates its relevance for calculating object properties necessary to manipulate objects independent of their identity or familiarity and monitor the online control of actions with these objects.

With the analysis of the interaction of object and task, we are able to isolate a network specifically relevant for tool use. This network includes the middle occipital gyrus close to V5 and clusters covering parts of the SMG, postcentral gyrus, and PMv of the left hemisphere. The areas are in line with the description of the ventro-dorsal stream (Binkofski and Buxbaum, 2013), which is suggested to run from the medial superior temporal area (MT/

Table 3. Group mean LIs for all conditions and brain lobes and *p* values of statistical test for significant laterality

	Frontal lobule		Parietal lobule		Temporal lobule		Occipital lobule		Sensorimotor cortex	
Condition	LI	*p*	LI	*p*	LI	*p*	LI	*p*	LI	*p*
Planning phase										
Tool use right	0.253	0.097	0.736	0.000*	0.533	0.000*	0.249	0.008*	0.740	0.000*
Tool transport right	0.589	0.000*	0.743	0.000*	0.454	0.001*	0.187	0.117	0.801	0.000*
Bar use right	0.396	0.000*	0.526	0.001*	0.282	0.019*	0.364	0.003*	0.623	0.000*
Bar transport right	0.124	0.328	0.519	0.000*	0.372	0.002*	0.318	0.013*	0.295	0.081
Tool use left	0.363	0.003*	0.574	0.000*	0.335	0.012*	0.074	0.549	0.603	0.000*
Tool transport left	0.436	0.001*	0.453	0.005*	0.273	0.065*	0.037	0.772	0.469	0.006*
Bar use left	0.179	0.123	0.344	0.001*	0.223	0.103	0.297	0.005*	0.413	0.005*
Bar transport left	0.301	0.009*	0.355	0.014*	0.262	0.050*	0.101	0.481	0.375	0.013*
Execution phase										
Tool use right	0.414	0.000*	0.288	0.009*	−0.323	0.004*	−0.073	0.543	0.543	0.000*
Tool transport right	0.172	0.181	0.134	0.276	−0.446	0.000*	−0.140	0.219	0.509	0.000*
Bar use right	0.511	0.000*	0.215	0.139	−0.263	0.024*	0.062	0.631	0.758	0.000*
Bar transport right	0.129	0.302	0.144	0.090	−0.338	0.003*	−0.055	0.654	0.430	0.000*
Tool use left	0.420	0.001*	0.561	0.000*	0.573	0.002*	0.604	0.001*	−0.064	0.664
Tool transport left	0.078	0.488	0.289	0.116	0.254	0.177	0.214	0.232	−0.144	0.247
Bar use left	0.263	0.032*	0.447	0.002*	0.462	0.011*	0.490	0.001*	−0.164	0.154
Bar transport left	−0.050	0.632	0.125	0.415	0.011	0.949	−0.090	0.584	−0.374	0.001*

*The mean LI value is significantly different from zero at a threshold of $p < 0.05$.

Table 4. Mean LIs for the levels of all factors and statistics for the test of main effects of factors[a]

			Frontal lobule		Parietal lobule		Temporal lobule		Occipital lobule		Sensorimotor cortex	
	Factor	Level	Mean LI	Statistics	Mean LI	Statistics	Mean LI	Statistics	Mean LI	Statistics	Mean LI	Statistics
Planning phase												
	Object	Tool	0.410	$p = 0.011$*	0.626	$p = 0.001$*	0.399	$p = 0.014$*	0.137	$p = 0.018$*	0.653	$p = 0.004$*
		Bar	0.250	$F = 8.46$	0.436	$F = 18.49$	0.285	$F = 7.66$	0.270	$F = 7.01$	0.426	$F = 11.51$
	Task	Use	0.298	$p = 0.327$	0.545	$p = 0.605$	0.343	$p = 0.945$	0.246	$p = 0.062$	0.594	$p = 0.051$*
		Transport	0.363	$F = 1.02$	0.517	$F = 0.28$	0.340	$F = 0.00$	0.161	$F = 4.06$	0.485	$F = 4.50$
	Hand	Right	0.340	$p = 0.853$	0.631	$p = 0.135$	0.410	$p = 0.374$	0.280	$p = 0.248$	0.615	$p = 0.253$
		Left	0.320	$F = 0.03$	0.431	$F = 2.49$	0.273	$F = 0.83$	0.127	$F = 1.44$	0.465	$F = 1.41$
Execution phase												
	Object	Tool	0.271	$p = 0.133$	0.318	$p = 0.025$*	0.014	$p = 0.534$	0.151	$p = 0.354$	0.211	$p = 0.232$
		Bar	0.213	$F = 2.52$	0.233	$F = 6.17$	−0.032	$F = 0.40$	0.102	$F = 0.91$	0.263	$F = 1.55$
	Task	Use	0.402	$p = 0.008$*	0.378	$p = 0.001$*	0.112	$p = 0.011$*	0.271	$p = 0.002$*	0.268	$p = 0.021$*
		Transport	0.082	$F = 9.42$	0.173	$F = 16.23$	−0.129	$F = 8.46$	−0.018	$F = 13.21$	0.105	$F = 16.63$
	Hand	Right	0.306	$p = 0.257$	0.195	$p = 0.432$	−0.342	$p = 0.001$*	−0.051	$p = 0.036$*	0.560	$p = 0.001$*
		Left	0.178	$F = 1.38$	0.356	$F = 0.65$	0.325	$F = 16.50$	0.305	$F = 5.32$	−0.186	$F = 52.85$

[a] Mean group laterality indices for levels of all factors and the *p* values and *F* values (df = 16) of the main effect of each factor.

*Significant main effect at a threshold of $p < 0.05$.

MST) to the inferior parietal lobule and the PMv (Rizzolatti and Matelli, 2003; Buxbaum and Kalénine, 2010; Binkofski and Buxbaum, 2013). It is thought to be important for processing the knowledge of specific learned object manipulations, such as tool use (Frey, 2008; Buxbaum and Kalénine, 2010). Especially parietal structures show strong influence in coding actions particularly related to tools (Valyear et al., 2007, 2012; Vingerhoets et al., 2009; Verhagen et al., 2012; Peeters et al., 2013). This also seems to be true for the PMv, which is suggested to monitor the hand posture relevant for actions with a tool (Vingerhoets et al., 2013). Patients suffering from apraxia, with difficulties in grasping and using tools or performing pantomime of use, usually have lesions in inferior parietal cortex and additionally inferior frontal areas (Goldenberg and Spatt, 2009; Kalénine et al., 2010; Randerath et al., 2010). Our results underline these findings and support the relevance of the ventro-dorsal pathway in tool use. Additionally, we show that it is coactivated with MTG, a ventral stream area. Its role in processing semantic information suggests a strong connection to the ventro-dorsal stream during goal-directed actions with known objects. All in all, we can show that both the dorso-dorsal but also the ventro-dorsal stream are activated with different ventral stream areas during actual object manipulations and tool use, which indicates that information from both ventral and dorsal stream has to be integrated for complex actions. A functional connection seems to be probable because structural connections between MTG and SMG have been found in a Diffusion Tensor Imaging study, which aimed to find structural connections between regions relevant for tool use pantomime (Ramayya et al., 2010). Further connectivity analysis would be needed to prove and investigate the influence of ventral stream areas on the dorsal pathway, especially during tool use.

The tool network during actual action planning and execution is largely common for dominant and nondominant hand

In our study, we are able to measure brain areas more active during planning and executing tool actions compared with performing goal-directed movements with neutral objects. The specific planning of tool manipulations recruits a mainly left-sided parietal and occipitotemporal network. Ventral stream activations in the LOC, MTG, and FG are relevant for object recognition and processing semantic knowledge of a tool (Milner and Goodale, 2008; Valyear and Culham, 2010). The left parietal cortex is known to be almost invariably involved in tool actions (Lewis, 2006). We show here that core regions of the parietal cortex (SPL, AIP, and SMG), essential for tool manipulations, are already recruited during preparation of actual execution. The relevance of the parietal cortex in action planning of grasping and using was emphasized by studies of Gallivan et al. (2011, 2013a, b) using pattern classification to decode movement intentions, as well as other literature focusing on planning of tool use pantomime (Johnson-Frey et al., 2005; Króliczak and Frey, 2009; Vingerhoets et al., 2011).

The execution of tool manipulations recruits a larger network with additional involvement of frontal areas, such as PMv, MFG, and insula. Frontal areas are known to be relevant for realizing motor plans, including grasping movements (Cavina-Pratesi et al., 2010; Gallivan et al., 2013a, 2013b) and executing tool use pantomime (Johnson-Frey et al., 2005; Króliczak and Frey, 2009; Vingerhoets et al., 2011).

A feature of the action network seems to be its left-sided asymmetry. Our results strongly support the finding that, in right-handers, planning and executing object manipulations is mainly processed by the left hemisphere, independent of the used hand. Interestingly, the lateralization is stronger while planning actions with tools than bars and for using compared with transporting during execution, which indicates a changing network structure during the time course of an action. Different from other studies (Moll et al., 2000; Choi et al., 2001; Króliczak and Frey, 2009; Jacobs et al., 2010), we found stronger activations during action execution with the nondominant hand compared with the dominant one. We assume that stronger left-sided activations are caused by an increase of recruitment of the action network in order for the untrained hand to perform as skilled and as dexterous as the right hand. Additionally, the unfamiliarity of left-hand actions might result in higher activations.

A new device to study neuronal processes of real actions

Our results provide direct evidence for the multifaceted nature of neural mechanisms underlying complex actions, such as tool use. This analysis was enabled by the use of a new device, the "Tool-Carousel," which allows studying the influence of different factors on real actions. The use of a mirror system in this study and the therefore added visual transformations create a limitation to the application, which should be avoided if the scanner environment allows it.

In conclusion, we successfully investigated actual tool and object manipulation using the "Tool-Carousel." We can identify activation patterns representing tool knowledge, goal-directed actions, object grasping, and manipulation of tools and objects, including frontal, parietal, and temporal centers. Preparatory activations were strongly lateralized to the left brain and remained active during actual task execution. Handling tools versus neutral bars and using an object versus transportation strengthen the lateralization of the action network toward the left brain. The results support the assumption that the dorso-dorsal pathway is relevant for monitoring the manipulated objects independent of prior knowledge about the object. On the other hand, regions of the ventro-dorsal pathway code the specific knowledge of how a known object (e.g., a tool) has to be used. Additionally, our study brings about the question of how exactly the ventral areas LOC and MTG connect with the two dorsal pathways during real actions and especially tool use.

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3 Age-related Changes in the Neural Correlates of Complex Object Manipulations.

The tool use network is mainly stable across age, but age-related neural changes have an influence on neural patterns of planning and executing tool use in elderly adults.

The manuscript included in this chapter is titled "Age-related changes in the neural correlates of complex object manipulations." and was written by Marie-Luise Brandi, Joachim Hermsdörfer, Chrisitan Sorg and Afra Wohlschläger. It describes another experimental study on actual tool use with mainly the same methodological procedure as described in chapter 2, but focusses on the neural underpinnings of real actions in elderly compared to young adults. It is currently unpublished and was submitted to the Journal of Neuroscience on December 31st 2014.

Contributions:

The author of this thesis is the first author of the manuscript. M.L.B., A.W., C.S. and J.H. designed research; M.L.B. performed research; M.L.B. and A.W. analyzed research; M.L.B., A.W., C.S. and J.H. wrote the paper.

Age-related Changes in the Neural Correlates of Complex Object Manipulations

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Abstract

Aging affects motor cognition such as complex actions like using objects as tools. However, neural aging effects on tool use are not yet understood. This study aims to analyze age-related changes of the neural correlates of planning and executing actions with known tools and neutral objects in a functional MRI experiment. Our analysis revealed three major findings describing complex actions in the aging brain: Major characteristics of the brain network involved in object manipulations remain stable in aging including its left-sided laterality and activations in temporal, parietal and frontal centers. Second, we find an age-related increase of neural activations during action planning – as expected - but unexpectedly activation decrease during action execution. Moreover, we demonstrate compensatory effects in the middle and inferior frontal gyrus as well as in the superior parietal occipital complex in elderly individuals. The Results provide evidence that while the action related network stays stable across age, the level of activation strength during the time course of an action is shifted towards the planning phase in elderly. Data suggest further a fronto-parietal compensatory mechanism in the aging brain to retain our ability to plan and control complex actions.

Introduction

We learn to use objects as tools very early in life and exercise this skill during our whole lifespan. Not being able to use tools properly, strongly constrains daily life routines. Due to common grey matter volume decline in aging (Courchesne et al., 2000; Good et al., 2001), but also because of neurological damages after a stroke (Goldenberg and Spatt, 2009), conducting complex actions can be impaired. In order to understand such behavioral changes, it is important to know and understand the neural basis of object manipulations in elderly adults.

Previous neuroimaging research on different cognitive processes in elderly showed that activation patterns are usually more bilateral and widespread compared to young adults (Cabeza, 2002). For the motor domain, elderly show an overall increase of brain activations and recruit additional brain areas compared to young adults to perform motor tasks (Mattay et al., 2002; Ward, 2003; Heuninckx et al., 2005, 2008; Ward et al., 2008; Noble et al., 2011). Another prominent effect of healthy aging is the reduction of selectivity in the elderly brain (Grady, 2002; Park et al., 2004). In order to explain the effect of stronger and less specified activation patters in the elderly two different theories exist. One describes the increased activation as a compensatory effect in which higher activations in elderly are necessary to perform as good as young adults (Mattay et al., 2002; Heuninckx et al., 2008; Spreng et al., 2010). On the other hand, the dedifferentiation theory argues that during aging specific brain functions are less bound to specific structures and that brain areas become less selective for different stimuli (Li et al., 2001; Logan et al., 2002; Carp et al., 2011; Park et al., 2011).

Based on previous findings on the aging brain we hypothesize that the neural process of complex object manipulation also underlies age-related changes. This target network relevant for object manipulation includes a robust pattern of brain regions including ventral stream, parietal and frontal areas (Johnson-frey et al., 2005; Lewis, 2006; Hermsdörfer et al., 2007; Vingerhoets et al., 2009; Valyear et al., 2012; Gallivan et al., 2013; Brandi et al., 2014). No study so far has investigated how the tool use network changes during healthy aging and whether possible mechanisms like dedifferentiation or compensation apply.

Therefore, the aim of this study was to investigate age-related changes in the brain network responsible for processing planning and execution of complex actions and analyze if underlying reasons for alterations can be explained by the existing theories. With the “Tool-Carousel” (Brandi et al., 2014), an apparatus used for the presentation of real objects during an fMRI experiment, we tested actual object manipulations in young and elderly adults. Of main interest were age-related differences during planning and execution of real actions. We expected more widespread and stronger brain activations in elderly adults. By including performance scores and a region of interest analysis we analyzed further, whether observed age-related changes were more compatible with the theories of compensation or dedifferentiation during actual object manipulations.

Methods

The basic experimental set up, procedure and data analysis methods in this study have been used and presented before in a previous study investigating the neural correlates of tool use in healthy young adults (Brandi et al., 2014). A short summary of these methods will be given here, but for detailed information see the previous article by Brandi et al. (2014). All changes and new analysis performed in this study will be described fully in the following sections.

Subjects

Twenty healthy elderly adults (8 female) and twenty healthy young adults (11 female) participated in the fMRI experiment. Before the experiment all subjects provided informed consent for the study, which was approved by the local ethical committee. Due to strong head movements, four elderly (2 female and 2 male) and three young adults (1 male and 2 female) had to be excluded from further statistical analysis. In order to have a balanced number of participants in both age groups one random young participant was excluded from the analysis, so both age groups included 16 participants. The data-set of young participants is partly overlapping with the data already presented in the previous study by Brandi et al. (2014) (overlap of 17 young adults). The mean age of included elderly participants was 67 years (age range 55 to 74 years) and 25 years (age range 21 to 28 years) of the young participants. All had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. The participants were all right-handed, as measured by the Edinburgh Handedness Inventory (Oldfield, 1971).

Experimental set up and design

The so-called "Tool-Carousel" was used to present real reachable and usable stimuli to the participants. In this study three different experimental factors were of interest: the type of object the participants had to manipulate, the type of manipulation done with the object and the age of the participants. The stimuli included ten different tools known from daily life and ten neutral objects. The color and shape of the neutral objects handles was chosen to match the different tools. The neutral objects were bar-shaped and for simplification, we refer to this stimuli set as "bars". The manipulation the participants had to perform was to either use the objects or to transport (meaning to grasp, lift and to return) them. The bars were marked in blue on one end and in order to use the bars, the blue end of the object had to be placed in a blue marked hole on the workspace. The tools had to be used as known from daily life experience. This resulted in 4 main conditions for both groups: 1) tool use; 2) tool transport; 3) bar use; 4) bar transport.

The experiment consisted of 200 trials which included 40 control trials (no stimulus or task cue was presented) and 160 condition trials. The time-course of a trial was separated in two different action phases: The planning phase, starting when the object and the cue for the task were visible to the participant; on the other hand the execution phase, which covered the actual movement of the action. The start of the execution phase was signaled with a green light, starting 2-6 sec after the planning phase and had a duration of 4 sec. Participants were asked to perform the task only when and while the green light was on. This action signal turned on only in half of the trials. The trials in which no green light was turned on were used to analyze the planning phase of an action. In these trials no movement occurred, which enabled us to analyze the planning of an action without any movement related activations. The analysis of the execution phase included the period in which the green light was turned on and the actual movement occurred. Because the onset of the green light varied, the participants could not predict if they would have to perform the action or not when they saw the stimuli.

We conducted one experimental run in which the participants had to use their non-dominant left hand to perform the task. Choosing only the non-dominant hand had two reasons: First, testing two runs, one with right-hand actions the other with left-hand actions, occurred to be too uncomfortable and exhausting for the elderly participants. Second, in our previous study we showed that real actions performed with the non-dominant left hand recruit the very same network as actions with the dominant right hand (except for the sensorimotor cortices). The only difference lies in the strength of activation, which is increased during actions with the non-dominant hand (Brandi et al., 2014). So the left hand was chosen to better differentiate between brain activity involved in planning and execution of object manipulations expected primarily in the left brain and primary motor activity in the contralateral right brain. In addition, the findings about the neural basis of real object manipulations in elderly can better be related to research on patients suffering from apraxia, who mostly use their non-paretic ipsi-lesional hand for actions of daily living.

Procedure

All participants had to answer a questionnaire before the start of the experiment. The questionnaire was used to check the participants' knowledge about the objects in the experiment and their familiarity with the usage. The maximum score testing the tool knowledge was 70 points (max. 7 points for each object). The maximum score of the questions testing the tool familiarity was 130 (max. 13 points for each object), which would indicate that all tools were used daily during the participant's job and daily routines. A score of 0 would mean that the object has never been used before by the participant and that the usage is not familiar to them. Two sample t-tests were calculated to measure possible differences in the scores between groups.

The tasks and cues of the experiment were explained to the participants with video instructions. All conditions were trained in the fMRI scanner until the participants were familiar with the tasks and capable to perform them. The Presentation Software (Neurobehavioral Systems, Inc.) was used to give acoustic instructions via headphones to the operator in the scanner room. The task cues and stimuli were exchanged by the operator for each trial and the "Tool-Carousel" was turned on the acoustic cues.

A camera recorded the workspace and hands of the participants during the whole experiment for behavioral evaluations.

Video analysis

The captured performance of the participants was rated by counting the errors made by the participants. We differentiated between three error types: 1) general task errors in which the task was not performed according to the cue; 2) grip errors - the objects were not grasped as shown in the instruction or known from daily routines; 3) movement errors - the movement of the action was not performed fully or according to the instructions.

Additionally the videos were analyzed with a motion detector (MATLAB based; Release 2012a, The MathWorks, Inc., Natick, Massachusetts, United States) to evaluate the duration of each movement of the participants from both age groups and the reaction times between the onset of the green light and the start of movement.

Of main interest were differences between the age groups, therefore two sample t-tests were calculated to measure possible differences.

MRI measurement

The MRI measurements were performed on a Siemens (Erlangen, Germany) 3 Tesla Verio MRI scanner. T1-weighted anatomical images were acquired with the MP-RAGE (magnetization-prepared rapid acquisition gradient echo) sequence. The blood oxygenation-level-dependent (BOLD) echo-planar images were measured using a T2*-weighted gradient echo sequence with the repetition time TR = 2000 ms, echo time TE = 30 ms, Field of View FoV = 192 mm, flip angle $\alpha = 90°$, matrix = 64 × 64, slices = 35, slice thickness = 3 mm and voxel size = 3mm × 3mm × 3mm.

fMRI Data Analysis

The entire data analysis was performed with SPM8 (Statistical Parametric Mapping software; The

Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). The fMRI data was preprocessed by using a slice time correction, realigning the images to correct for movement artifacts, coregistering the anatomical and normalizing all images to standard space (Montreal Neurological Institute, see SPM software). Thereafter, the functional data sets were smoothed with a Gaussian kernel of 8 mm for group analysis.

The statistical analysis was done first on a single subject first level and then at group level in a second level factorial analysis. A general linear model (GLM) was calculated for each subject with 15 regressors including a separate regressor for all planning phases and the execution phases of the trials which included the action signal (green light) of all 4 condition respectively (12 regressors in total), a regressor for the control condition, one covering the duration of all movements and one regressor modeling the individual errors of the participants. Additionally the realignment movement parameters were entered into the model to correct for any motion related artifacts in both groups.

The second level was analyzed separately for the planning and execution phase in a 2 x 2 x 2 factorial design with the factors object (tool and bar), task (use and transport) and group (elderly and young) in which the main effects of the factors object and task for each group separately and the main effect for the factor group are of most interest. The interactions object*group and task*group were also calculated to test dedifferentiation effects as it is described below.

The Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to label the activated brain areas. The graphical display was realized with the BrainNet toolbox (Xia et al., 2013) to show the statistical maps on 3D rendered brain models and with MRIcron (Rorden et al., 2007) to show them on a selection of 2D brain slices.

Voxel based morphometry

Brain atrophy is well-known in healthy aging and leads to decreased grey and white matter volumes. To review any structural changes in our sample and to control all functional results for structural alterations we conducted a voxel based morphometry analysis (VBM). To get the individual tissue volumes, the structural images of all participants were segmented into the three tissue types (grey matter, white matter and cerebral spinal fluid (CSF)) and the volumes were estimated with the help of the VBM 8 toolbox (Ashburner and Friston, 2000). The default options for a basic VBM analysis were chosen as suggested by the developers of the toolbox. The created grey matter segments, which were modulated for non-linear components, were smoothed with an 8 mm kernel FWHM to enter the second level analysis. To find the brain areas in which the grey matter volume is related with age, a regression analysis with the covariate “age” was conducted.

In order to control for age-related structural differences in the functional analysis, a voxel-wise regression with the participants individual grey matter maps and the contrast images for the factorial analysis was conducted before the images entered the previously mentioned factorial second level analysis (Bäuml et al., 2014). Therefore any group effects in the analysis of the functional data are corrected for effects of atrophy on the grey matter activation due to healthy aging.

Testing compensatory effects in the elderly – A multiple regression analysis

Previous studies (Heuninckx et al., 2008) showed that good performance in a simple motor task positively correlates with the level of brain activation in elderly individuals and interpret this as a compensatory mechanism. To test, if this theory can also be applied to complex actions including object manipulations, we used a within-group multiple regression following the approach of Heuninckx et al. (2008). The subjects individual contrast images comparing all conditions versus the control condition entered the multiple regression analysis. The behavioral measure describing the performance and the age of the participants (the latter as a covariate of no interest) entered the analysis. The performance score comprised the total amount of errors of the different error types each participant made. This total error score yielded a sufficiently broad distribution varying between 0 and 7 errors within the group of elderly subjects. Therefore a negative correlation between the performance score and the activation strength indicates an increased brain activity with better performance, which can be interpreted as a compensatory mechanism. The multiple regression analysis was done for the planning and execution phase separately in a whole brain analysis. To illustrate the relation of behavior and brain activity, the activation data of the brain areas resulting from the multiple regression analysis of the elderly were extracted with the Marsbar toolbox as 6 mm spheres around the MNI coordinate of the peak voxels (Brett et al. 2002) and plotted in relation to the performance. In order to compare these findings with the young adults the activation data of the same brain areas was also extracted and plotted from the young adults. Pearson correlation coefficients were calculated for all brain areas for both groups, to conduct a statistical comparison. A Fisher`s Z-transformation of the correlation coefficients was performed to calculate the Z-difference and evaluate statistical differences of the correlation coefficient between groups.

Testing dedifferentiation effects in the elderly – A region of interest analysis

In order to test if brain areas in the elderly are less selective for a given task, the interaction object*group and task*group were calculated. A significant interaction could result, if the young adults show a higher activation difference between the levels of different factors, than the elderly adults. Such finding can be interpreted as a dedifferentiation effect (Grady, 2012). Because a whole brain analysis is not a sensitive method to test these effects, we additionally conducted a region of interest (ROI) analysis which reduces the number of voxels tested and limits the analysis to relevant brain areas. We chose to examine dedifferentiation effects in regions that were shown before to be selective for the manipulation of tools and bars and the task use and transport in a whole brain analysis in healthy young adults. The exact anatomical locations of the ROIs were selected from our previous work and included the lateral occipital complex (LOC; MNI coordinates: x = -42, y = -70, z = 7), middle temporal gyrus (MTG; MNI coordinates: x = -60, y = -61, z = 10), supramarginal gyrus (SMG; MNI coordinates: x = -60, y = -25, z = 46), superior parietal lobe (SPL; MNI coordinates: x = -18, y = -67, z = 52), superior parietal occipital complex (SPOC; MNI coordinates: x = -9, y = -76, z = 34), middle occipital gyrus (MOG; MNI coordinates: x = -36, y = -85, z = 25), IPL (MNI coordinates: x = -57, y = -31, z = 52), dorsal premotor cortex (PMd; MNI coordinates: x = -21, y = 8, z = 64), ventral premotor cortex (PMv; MNI coordinates: x = -48, y = 5, z = 28) and the insula (MNI coordinates: x = -30, y = 20, z = 4) (Brandi et al., 2014). Several other studies have reported these brain areas to be distinctively active for different types of actions in young adults (Culham et al., 2003; Vingerhoets et al., 2010; Gallivan et al., 2013; Monaco et al., 2013). In our previous study the chosen ROIs showed higher activations for actions with tools compared to bars and a subset of regions (SPL, PMd, SPOC, LOC) also showed higher activity for the condition use compared to transport in young adults. To extract the data from these brain areas, ROI-masks were creates as 6 mm spheres around the given MNI coordinate with the toolbox Marsbar (Brett et al., 2002). Marsbar was also used to extract the data from each individual participant, which then entered a factorial analysis (IBM SPSS Statistics; IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) including the factors object and task as within-subject and the factor group as a between-subject variable and tested for object*group and task*group interactions (comparable to the analysis by Park et al., 2004).

Laterality Index

In order to measure and test the lateralization of the analyzed networks, the laterality index (LI) was calculated with the LI toolbox (Wilke and Lidzba, 2007) for each subject and all conditions, separately. A t-test was performed for each group to evaluate if the LIs of all conditions are significantly different form 0 (a LI of zero would indicate a symmetrical activation pattern). The analysis was performed for the frontal, parietal, temporal, occipital and sensorimotor cortices separately. Additionally two-sample t-tests were conducted to evaluate possible group differences in the lateralization of brain networks.

Results

Behavioral results: Questionnaire – Tools are comparably known across groups

The questionnaire aimed to measure the participants object knowledge and their familiarity of object usage to make sure all tools, but not the bars, were known by the participants. Additionally, it was of interest if the scores of the two groups differ. The scores of the questionnaire and p-values of the group comparisons are listed in Table 1. The data demonstrate that both age groups knew all tools and were similarly familiar with their usage, while both groups did not know nor were familiar with the bars.

Table 1: Behavioral scores and statistics of the comparisons between groups

	Tool Knowledge		**Tool Familiarity**		**Score neutral Object**		**Mistakes Grip**		**Mistakes Movement**		**Task error**		**Mistakes total**		**Movement Duration**		**Reaction Time**	
	median	**p-value**	**median**	**p-value**	**median**	**p-value**	**median**	**p-value**	**median**	**p-value**	**median**	**p-value**	**median**	**p-value**	**mean [sec]**	**p-value**	**mean [sec]**	**p-value**
Elderly	70 (66-70)	0.434	98 (68-125)	0.108	0 (0-2)	0.8	1.5 (0-3)	0.012*	1 (0-3)	0.115	1 (0-6)	0.018*	4 (0-7)	0.0005*	4.144 (±0.453)	0.648	0.557 (±0.192)	0.158
Young	70 (66-70)		94 (73-111)		0 (0-3)		0 (0-3)		0 (0-3)		0 (0-2)		1 (0-5)		4.105 (±0.485)		0.517 (±0.098)	

The range of all scores is given in parentheses behind the mean value. Indicated with a star (*) are significant p-values.

Behavioral results: Video analysis – More grip and task errors in elderly adults

In the video analysis the performance of the participants and the movement duration and reaction times were measured and tested for group differences. The median error scores of the grip errors, movement errors, task errors and the total amount of errors are listed in Table 1 together with the p-value of the group comparison. The elderly individuals made significantly more grip and task errors compared to the young adults which also resulted in a significant difference in the total error score.

The results of the motion detection analysis are also listed in Table 1 and show that both groups showed similar reaction times and took a similar amount of time to perform the actions.

Voxel Based Morphometry – A typical atrophy pattern in elderly adults

In order to measure differences in the grey matter volume between the groups, a VBM analysis and a regression analysis were calculated. This analysis evaluates the differences in brain structure and detects those brain areas in which decreased grey matter volume is associated with higher age. Figure 1 shows the tissue volumes of white, grey matter and the CSF of both groups. Two sample t-tests revealed that the grey matter volume is significantly smaller ($p = 0.0003$) and that the CSF is significantly larger ($p <$

0.0001) in the elderly adults. The results of the regression analysis are shown in Figure 2 at a threshold of $p < 0.05$ including a FWE correction for multiple comparisons. Table 2 lists all brain areas which grey matter volume show a significant negative relation with age, meaning a decreased volume with increased age (Good et al., 2001).

Brain areas with the highest age dependent grey matter volume decrease are the insula cortex, inferior frontal gyrus (pars. orbitalis), inferior frontal gyrus (pars. triangularis) and the SMG in the left hemisphere and the putamen and insula in the right hemisphere. In general, a correlation can be seen in all brain lobes in both hemispheres also in brain areas which are known to be relevant in object manipulations. Because the differences in grey matter volume could confound the functional activation analysis, the effects of varying grey matter volumes are regressed out as described in the methods section. Therefore, the following results are not confounded with effects of the age-related grey matter volume decreases.

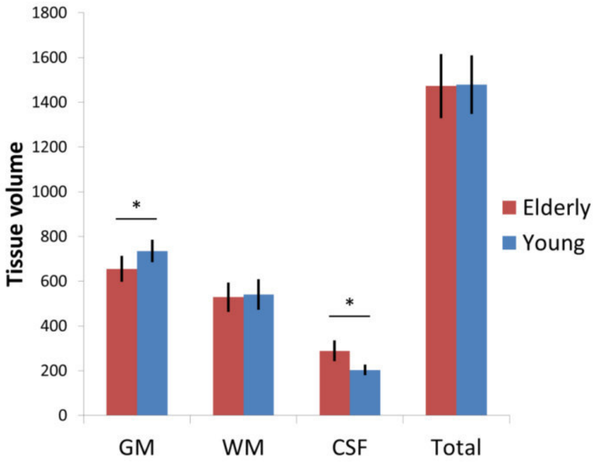

Figure 1: Tissue volume of elderly (blue) and young (red) for grey matter (GM), white matter (WM), cerebral spinal fluid (CSF) and total volume. The star (*) indicates a significant difference between the group.

Figure 2: Statistical map of the VBM regression analysis shown on transversal brain slices ($z = -40, -30, -20, -10, 0, 10, 20, 30, 40, 50$ and 60). Shown are brain areas which decreased grey matter volume correlates with increasing age at a threshold of $p < 0.05$ (FWE corrected).

Table 2: Results of the VBM regression analysis including the anatomical locations and p-values of the peak voxels. Reported are only brain areas with $p < 0.05$ (FWE corrected).

Brain Areas - Left Hemisphere	p-value	Brain Areas - Right Hemisphere	p-value
Frontal Lobe		**Frontal Lobe**	
Anterior Cingulate Cortex	0.0082	Anterior Cingulate Cortex	0.0234
Inferior Frontal Gyrus	0.0022	Inferior Frontal Gyrus - PMv	0.0146
Inferior Frontal Gyrus - PMv	0.0124	Inferior Frontal Gyrus (pars. Orbitalis)	0.0084
Inferior Frontal Gyrus (pars. Orbitalis)	0.0178	Midcingulate Cortex	0.0010
Midcingulate Cortex	0.0313	Orbital Gyrus	0.0019
Middle Frontal Gyrus	0.0337	Rolandic Operculum	0.0050
Orbital Gyrus	0.0027	Superior Frontal Gyrus	0.0104
Superior Frontal Gyrus	0.0049	**Insula Cortex**	
Insula Cortex		Insula	0.0054
Insula	0.0030	**Occipital Lobe**	
Parietal Lobe		Middle Occipital Gyrus	0.0006
Inferior Parietal Lobe	0.0186	**Parietal Lobe**	
Postcentral Gyrus	0.0005	Angular Gyrus	0.0026
SupraMarginal Gyrus	0.0038	Inferior Parietal Lobe	0.0016
Temporal Lobe		Postcentral Gyrus	0.0195
Fusiform	0.0279	Precuneus	0.0007
Middle Temporal Gyrus	0.0160	SupraMarginal Gyrus	0.0100
Superior Temporal Gyrus	0.0297	**Temporal Lobe**	
Superior Temporal Pole	0.0155	Fusiform	0.0169
		Middle Temporal Gyrus	0.0029
		Superior Temporal Gyrus	0.0001
		Superior Temporal Pole	0.0068
		Subcortical	
		Putamen	0.0023

Within-subject analysis for factor object and task in elderly and young during planning and execution

To characterize those brain areas relevant for planning and executing complex actions with objects for both age groups, the main effects for the factors object and task were calculated by comparing the conditions tool vs. bar and use vs. transport, respectively. This was done for both groups and for planning and execution phase separately. First presented are the results of the planning phase in elderly and young adults. Figure 3 A shows the brain maps of the elderly on the left and the young adults on the right for the two mentioned contrasts. Results are shown at a threshold of $p < 0.05$ including a FWE correction at the cluster-level. The calculated contrast tool vs. bar shows a left lateralized activation pattern for both age groups including occipital, temporal and parietal regions. The LOC, MOG, SMG and parts of the anterior intraparietal area (AIP) show a significant difference in the activation strength in both elderly and young adults. The left and right SPL survive the threshold only in young adults. Comparing the conditions use vs. transport resulted in a significant difference only in the left PMd in the elderly adults. In the young adults no significant voxels survived the applied threshold of $p < 0.05$ including a FWE correction at the cluster-level (Figure 3 A lower panel on the right). A list of the anatomical locations of the peak voxels are given in Table 3 together with the p-values.

The same analysis was performed for the execution phase and is shown in Figure 3 B also at a threshold of $p < 0.05$ including a FWE correction at the cluster-level. The comparison tool vs. bar reveals a similar pattern of activation in both groups with significant differences in clusters mainly of the left occipital, temporal, parietal, frontal and insula cortex. As also obvious for the planning phase, elderly show fewer activated areas at the given threshold. The MOG, parts of the SPL, PMd and the middle frontal gyrus (MFG) do not show a significant difference between the manipulations of tools compared to bars in elderly above threshold. The comparison use vs. transport for action execution shows no significant difference for the elderly individuals but activations in the LOC, SPL, poscentral gyrus (PoG), precentral gyrus (PrG), aIPA and PMd in the young adults (Fig 3 B lower panel on the right). The anatomical locations of these results are listed in Table 3 together with the p-values.

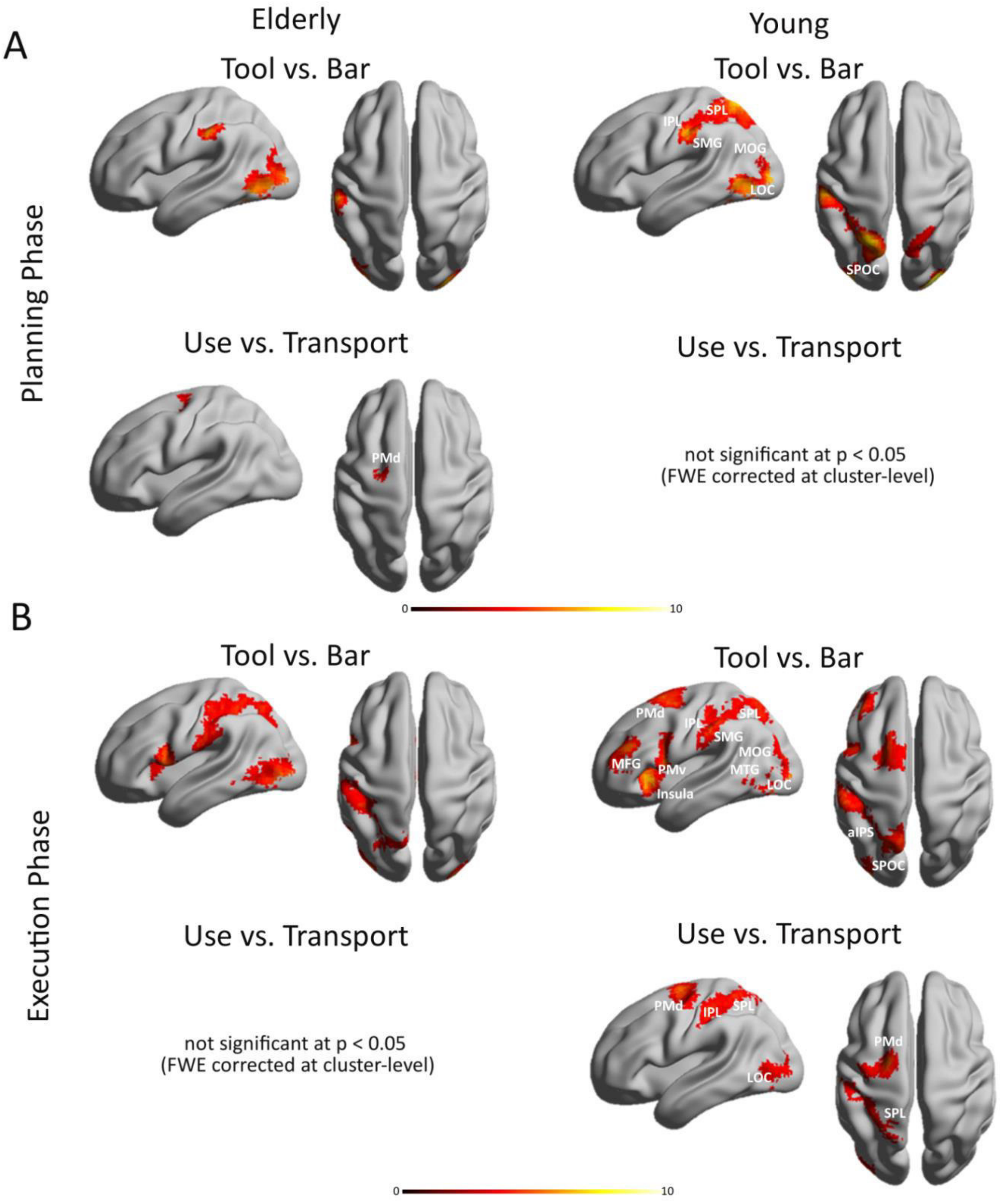

Figure 3: Whole brain results for the main contrast of the factor object and task for both age groups separately. **A)** The activation map of the planning phase for the contrast tool vs. bar is shown in the upper panel for the elderly on the left and for the young adults on the right side. In the lower panel the activation map for the contrast use vs. transport is shown for the elderly on the left side. The young adults show no significant voxels at the given threshold. **B)** The activation map of the execution phase for the contrast tool vs. bar is shown in the upper panel for the elderly on the left and the young adults on the right side. In the lower panel the activation map for the

contrast use vs. transport is shown for the young adults on the right side. The elderly adults show no significant voxels at the given threshold. All results of Figure 3 are shown at a threshold of $p < 0.05$ (FWE corrected at the cluster-level). The color scale under the brain images indicates the range of the T-values from low values in dark red to high values in white. Abbreviations: inferior parietal lobe (IPL), lateral occipital complex (LOC), middle frontal gyrus (MFG), middle temporal gyrus (MTG), middle occipital gyrus (MOG), superior parietal occipital complex (SPOC), dorsal premotor cortex (PMd), ventral premotor cortex (PMv), supramarginal gyrus (SMG), superior parietal gyrus (SPL).

Table 3: Results of the factorial analysis for both groups during planning and execution phase including the anatomical locations and p-values of the peak voxels. Reported are only those brain areas with $p < 0.05$ (FWE corrected at a cluster-level).

	Planning Phase			**Execution Phase**		
	Tool vs. Bar		**Use vs. Transport**	**Tool vs. Bar**		**Use vs. Transport**
Brain Areas	**Elderly**	**Young**	**Elderly**	**Elderly**	**Young**	**Young**
Left Hemisphere						
Frontal Lobe						
Inferior Frontal Gyrus - PMv				0.0000	0.0000	
Inferior Frontal Gyrus (pars. Triangularis)				0.0000	0.0025	
Midcingulate Cortex					0.0001	
Middle Frontal Gyrus					0.0025	
Precentral Gyrus					0.0000	0.0020
Rolandic Operculum				0.0000		
Superior Frontal Gyrus					0.0001	
Superior Frontal Gyrus - PMd			0.0094		0.0001	0.0020
Supplementary Motor Area			0.0094		0.0001	
Insula Cortex						
Insula				0.0000	0.0000	
Occipital Lobe						
Inferior Occipital Gyrus	0.0000			0.0001	0.0010	0.0136
Inferior Occipital Gyrus - LOC	0.0000	0.0000			0.0010	0.0136
Lingual Gyrus	0.0000	0.0000				
Middle Occipital Gyrus	0.0000	0.0000		0.0001	0.0010	0.0136
Parietal Lobe						
Anterior Intraparietal Area		0.0000		0.0000		
Inferior Parietal Lobe	0.0057	0.0000		0.0000	0.0000	0.0004
Postcentral					0.0000	
Postcentral Gyrus				0.0000		
Precuneus				0.0000	0.0000	0.0004
Superior Parietal Gyrus		0.0000		0.0000	0.0000	
Superior Parietal Lobe		0.0000				0.0004
Superior Parietal Lobe - SPOC		0.0000		0.0000	0.0000	0.0004

	Planning Phase			Execution Phase		
	Tool vs. Bar		Use vs. Transport	Tool vs. Bar		Use vs. Transport
Brain Areas	**Elderly**	**Young**	**Elderly**	**Elderly**	**Young**	**Young**
SupraMarginal Gyrus	0.0057			0.0000	0.0000	
Temporal Lobe						
Fusiform Gyrus	0.0000	0.0000				
Inferior Temporal Gyrus	0.0000			0.0001		
Middle Temporal Gyrus	0.0000	0.0000		0.0001	0.0010	0.0136
Superior Temporal Gyrus				0.0000		
Superior Temporal Pole					0.0000	
Subcortical						
Amygdala				0.0000		
Hippocampus				0.0000		
Pallidum				0.0000		
Putamen				0.0000		
Thalamus				0.0000		
Right Hemisphere						
Frontal Lobe						
Supplementary Motor Area					0.0001	
Occipital Lobe						
Calcarine Gyrus		0.0002		0.0465		
Inferior Occipital Gyrus				0.0465		
Middle Occipital Gyrus	0.0007			0.0465		
Parietal Lobe						
Superior Parietal Lobe		0.0120				
Superior Parietal Lobe - SPOC		0.0120				
Temporal Lobe						
Fusiform Gyrus		0.0198				

Group comparison of object manipulations during planning and execution – Differences in activation strength for both phases between groups

One main focus of this study was to evaluate possible age-related difference between the groups. Therefore we also conducted a direct comparison of the elderly and young adults including all experimental conditions during action planning and execution, respectively. Figure 4 A shows the activation maps of those brain regions with higher activation strengths in elderly compared to the young adults during action planning in the upper panel on the left. These brain areas include the left prefrontal cortex (in the MFG), left and right inferior frontal gyrus (IFG, PMv) in the PMv, PrG, IPL, SMG, SPOC, MTG and LOC. The reverse contrast did not reveal any significant results at the given threshold ($p < 0.05$, FWE corrected at cluster-level) as indicated in Figure 4 A on the right upper panel.

The same was analyzed for the execution phase and resulted in significant activation differences only in the comparison young vs. elderly (Figure 4 A lower panel on the right). Mainly frontal brain areas, the cingulate gyrus, sensorimotor cortices and SPL showed higher activations in young adults during action execution compared to the elderly. The reverse contrast did not reveal any significant results as indicated in Figure 4 A in the lower panel on the left. The location of the peak voxels including the p-values of the group comparisons are listed in Table 4.

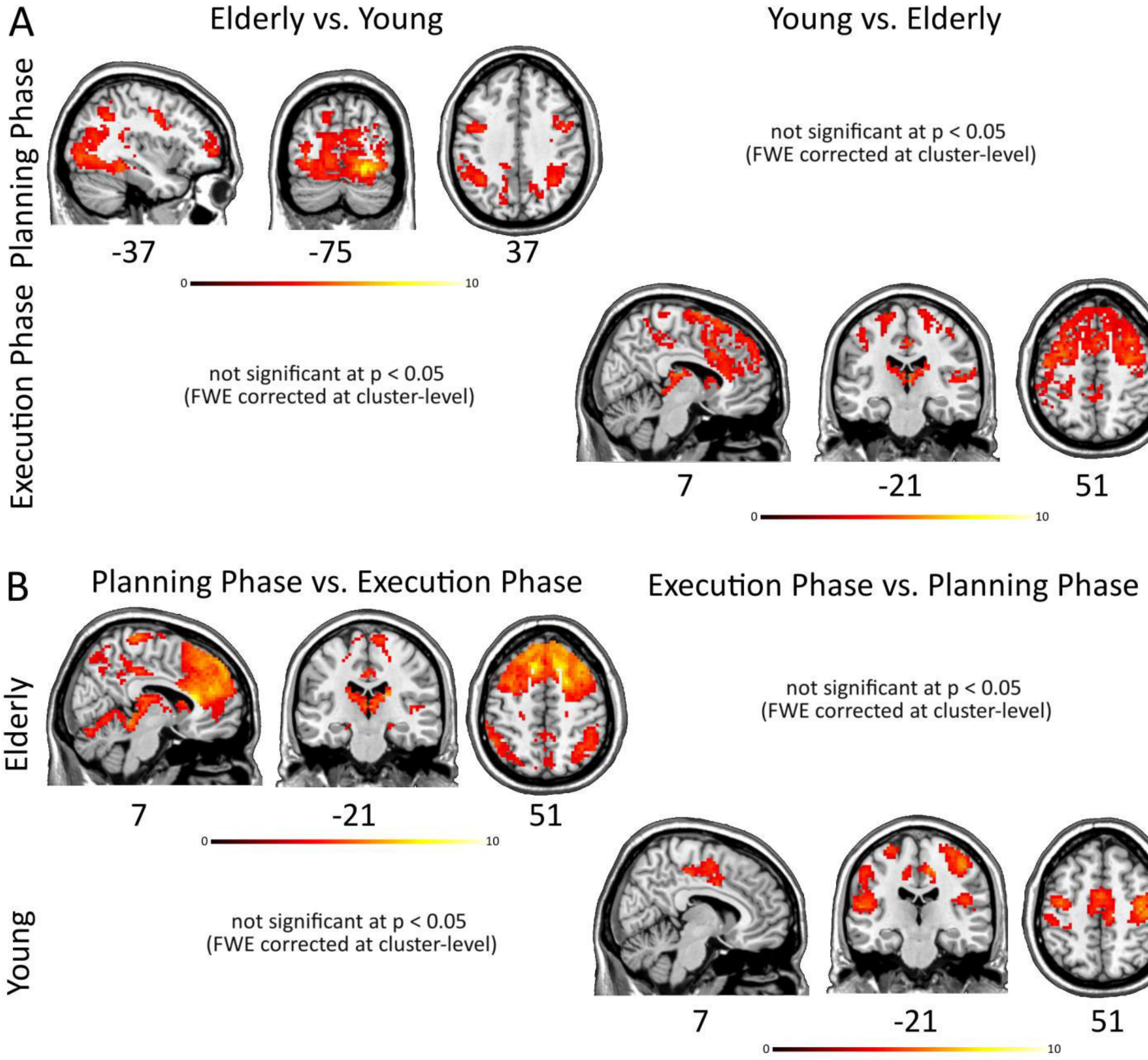

Figure 4: Results of the group comparison for both planning and execution phase and the comparison between phases within the group. A) Activation maps for the group comparisons elderly vs. young and young vs. elderly for the planning phase in the upper panel and the execution phase in the lower panel. The activation maps are shown on sagittal, coronal and transversal brain slices. The slice numbers (in MNI space) are indicated below the brain slice. B) Activation maps for the comparison between phases (planning phase vs. execution phase on the left side and execution phase vs. planning phase on the right side) within each age group. The results of the elderly are

shown in the upper and the results of the young adults in the lower panel. All results of Figure 4 are shown at a threshold of $p < 0.05$ (FWE corrected at the cluster-level). The color scale under the brain images indicates the range of the T-values from low values in dark red to high values in white.

In order to evaluate possible reasons for these group differences for planning and execution, we conducted another factorial analysis with the factor phase (including the level planning phase and execution phase) and the factor group. This analysis enabled us to examine differences between phases within the groups which might be related to the presented group comparison results. The activation maps of the comparisons planning phase vs. execution phase and the reverse contrast for the elderly adults are shown in Figure 4 B in the upper panel at $p < 0.05$ FWE corrected at the cluster-level. Only the contrast planning phase vs. execution phase revealed significant results at the given threshold in elderly adults. As in the previously described result of the comparison young vs. elderly, during action execution frontal brain areas, the cingulate gyrus, sensorimotor cortices and SPL showed a significant difference in the comparison planning phase vs. execution phase. Therefore, a possible reason for higher activations in the young adults during action execution is that elderly reduce the strength of activation during this phase compared to action planning. The same comparisons were done for the young adults and revealed significant differences only in the comparison execution phase vs. planning phase. The sensorimotor cortex, SMA and the basal ganglia show a significant difference in activation strength at $p < 0.05$ (FWE corrected at a cluster level) in Figure 4 B in the lower panel. A list of the anatomical location of all significant brain areas and the p-values are given in Table 4.

Table 4: Results of group comparison during planning and execution phase, the multiple regression analysis and the comparison of phases within the groups. Included are the anatomical locations and p-values of the peak voxels. Reported are only those brain areas with $p < 0.05$ (FWE corrected at a cluster-level).

	Planning Phase	**Execution Phase**	**Planning Phase**	**Execution Phase**	**Elderly**	**Young**
Brain Areas	**Elderly vs. Young**	**Young vs. Elderly**	**Compensation Effect**	**Compensation Effect**	**Planning Phase vs. Execution Phase**	**Execution Phase vs. Planning Phase**
Left Hemisphere						
Frontal Lobe						
Anterior Cingulate Cortex		0.0000			0.0000	
Inferior Frontal Gyrus - PMv		0.0000			0.0000	
Inferior Frontal Gyrus (pars. Orbitalis)					0.0000	
Inferior Frontal Gyrus (pars. Triangularis)		0.0000			0.0000	
Midcingulate Cortex		0.0000			0.0000	0.0000
Middle Frontal Gyrus	0.0041	0.0000	0.0006		0.0000	
Orbital Gyrus					0.0000	
Posterior Cingulate Cortex	0.0000				0.0000	
Precentral Gyrus	0.0014	0.0000		0.0466	0.0000	0.0000
Rolandic Operculum						0.0000

	Planning Phase	Execution Phase	Planning Phase	Execution Phase	Elderly	Young
Brain Areas	**Elderly vs. Young**	**Young vs. Elderly**	**Compensation Effect**	**Compensation Effect**	**Planning Phase vs. Execution Phase**	**Execution Phase vs. Planning Phase**
Superior Frontal Gyrus	0.0041	0.0000			0.0000	
Superior Frontal Gyrus (medial)		0.0000			0.0000	
Supplementary Motor Area		0.0000			0.0000	0.0000
Insula Cortex						
Insula					0.0000	
Occipital Lobe						
Calcarine Gyrus	0.0000				0.0000	
Cuneus	0.0000					
Inferior Occipital Gyrus	0.0000					
Inferior Occipital Gyrus - LOC	0.0000					
Lingual Gyrus	0.0000				0.0000	
Middle Occipital Gyrus	0.0000				0.0000	
Superior Occipital Gyrus					0.0000	
Parietal Lobe						
Angular Gyrus	0.0000				0.0000	
Inferior Parietal Lobe	0.0000	0.0000			0.0000	0.0000
Postcentral Gyrus		0.0000			0.0000	0.0000
Precuneus	0.0000	0.0000			0.0000	
Superior Parietal Lobe	0.0000	0.0000			0.0000	
Superior Parietal Lobe - pIPS			0.0257			
Superior Parietal Lobe - SPOC			0.0261			
SupraMarginal Gyrus	0.0000				0.0000	0.0000
Temporal Lobe						
Fusiform Gyrus	0.0000				0.0000	
Inferior Temporal Gyrus	0.0000					
Middle Temporal Gyrus	0.0000					
Superior Temporal Gyrus	0.0000					0.0000
Subcortical						
Caudate		0.0000	0.0438		0.0000	
Putamen		0.0000			0.0000	
Thalamus	0.0000	0.0000			0.0000	
Right Hemisphere						
Frontal Lobe						
Anterior Cingulate Cortex		0.0000			0.0000	
Inferior Frontal Gyrus - PMv	0.0017	0.0000			0.0000	
Inferior Frontal Gyrus (pars. Orbitalis)		0.0000			0.0000	
Inferior Frontal Gyrus (pars. Triangularis)		0.0000			0.0000	
Midcingulate Cortex		0.0000		0.0012	0.0000	0.0000

Brain Areas	Planning Phase	Execution Phase	Planning Phase	Execution Phase	Elderly	Young
	Elderly vs. Young	Young vs. Elderly	Compensation Effect	Compensation Effect	Planning Phase vs. Execution Phase	Execution Phase vs. Planning Phase
Middle Frontal Gyrus	0.0017	0.0000	0.0044		0.0000	
Orbital Gyrus					0.0000	
Posterior Cingulate Cortex	0.0000	0.0000			0.0000	
Precentral Gyrus	0.0017	0.0000		0.0060	0.0000	0.0000
Rolandic Operculum		0.0095			0.0000	0.0303
Superior Frontal Gyrus		0.0000			0.0000	
Superior Frontal Gyrus (medial)		0.0000			0.0000	
Supplementary Motor Area		0.0000			0.0000	
Insula Cortex						
Insula		0.0095			0.0000	
Occipital Lobe						
Calcarine Gyrus	0.0000					
Cuneus	0.0000			0.0003		
Inferior Occipital Gyrus					0.0000	
Lingual Gyrus	0.0000	0.0000		0.0409	0.0000	
Middle Occipital Gyrus	0.0000			0.0248		
Superior Occipital Gyrus	0.0000				0.0000	
Parietal Lobe						
Angular Gyrus	0.0000				0.0001	
Inferior Parietal Lobe	0.0000	0.0000			0.0001	
Postcentral Gyrus		0.0000			0.0000	
Precuneus	0.0000	0.0000		0.0101	0.0000	
Superior Parietal Lobe	0.0000	0.0000			0.0000	0.0303
Superior Parietal Lobe - SPOC				0.0004		
SupraMarginal Gyrus		0.0000			0.0001	
Temporal Lobe						
Fusiform Gyrus	0.0000				0.0000	
Inferior Temporal Gyrus	0.0000				0.0000	
Middle Temporal Gyrus	0.0000				0.0000	
Middle Temporal Pole					0.0000	
Superior Temporal Gyrus	0.0000	0.0095			0.0000	
Superior Temporal Pole		0.0095			0.0000	
Subcortical						
Caudate		0.0000			0.0000	
Putamen		0.0000			0.0000	
Thalamus		0.0000			0.0000	

Multiple regression analysis - Compensatory effects in the elderly

To test possible age related compensators effects a multiple regression analysis was performed for the elderly which tests if performance is related to activation strength. This analysis was done for both planning and execution phase. The brain areas showing a significant negative correlation (meaning increased activation while performing fewer errors) are depicted in Figure 5 for the planning phase. A cluster in both the left and right middle frontal gyrus (MFG) reaching to the inferior frontal gyrus and PMv was found, as well as a small cluster in the area of the left parieto-occipital junction at the SPOC and the posterior part of the intraparietal sulcus (pIPS). The same analysis in the execution phase showed a significant negative correlation in the right SPOC, precuneus, posterior cingulate cortex and the right and left PrG (Figure 5). A list of the anatomical locations and p-values are given in Table 4. The graphs in Figure 5 C and D plot the number of errors in relation to the activation strength and illustrate the negative correlation in the elderly. The comparison of the correlation coefficients between groups revealed a significant difference between correlations of elderly and young adults ($p < 0.05$) for all brain regions during action planning (right MFG: $p = 0.004$; left MFG: $p = 0.013$; left SPOC: $p = 0.025$; left pIPS: $p = 0.007$), but not for action execution (right precuneus: $p = 0.432$; right posterior cingulate cortex: $p = 0.946$; right SPOC: $p = 0.886$; left precentral gyrus: $p = 0.372$; right precentral gyrus: $p = 0.988$;).

Region of interest analysis – Fine dedifferentiation effects in the elderly

In order to test the dedifferentiation hypothesis for the whole brain, interactions between the factors group with object or task were calculated. Interactions in brain areas showing a higher difference between conditions in the young compared to the elderly were of interest. No significant interactions were found in the whole brain analysis for both action planning and execution. The ROI-analysis on the other hand, which included those areas, showing significant differences between conditions in the young adults in our previous study, revealed a dedifferentiation effect during action planning in the left SPL for the interaction object*group ($F(1, 30) = 5.502$; $p = 0.026$). In exact, this interaction is characterized by a higher activation difference between the condition tool and bar in the young (activation strength of 2.59 [range 1.65 – 3.5] for the condition tool and 0.55 [range -0.33 – 1.43] for the condition bar) compared to the elderly (activation strength of 2.92 [range 1.98 – 3.87] for the condition tool and 1.95 [range 1.07 – 2.84] for the condition bar). There was no significant interaction found in any of the other tested ROIs.

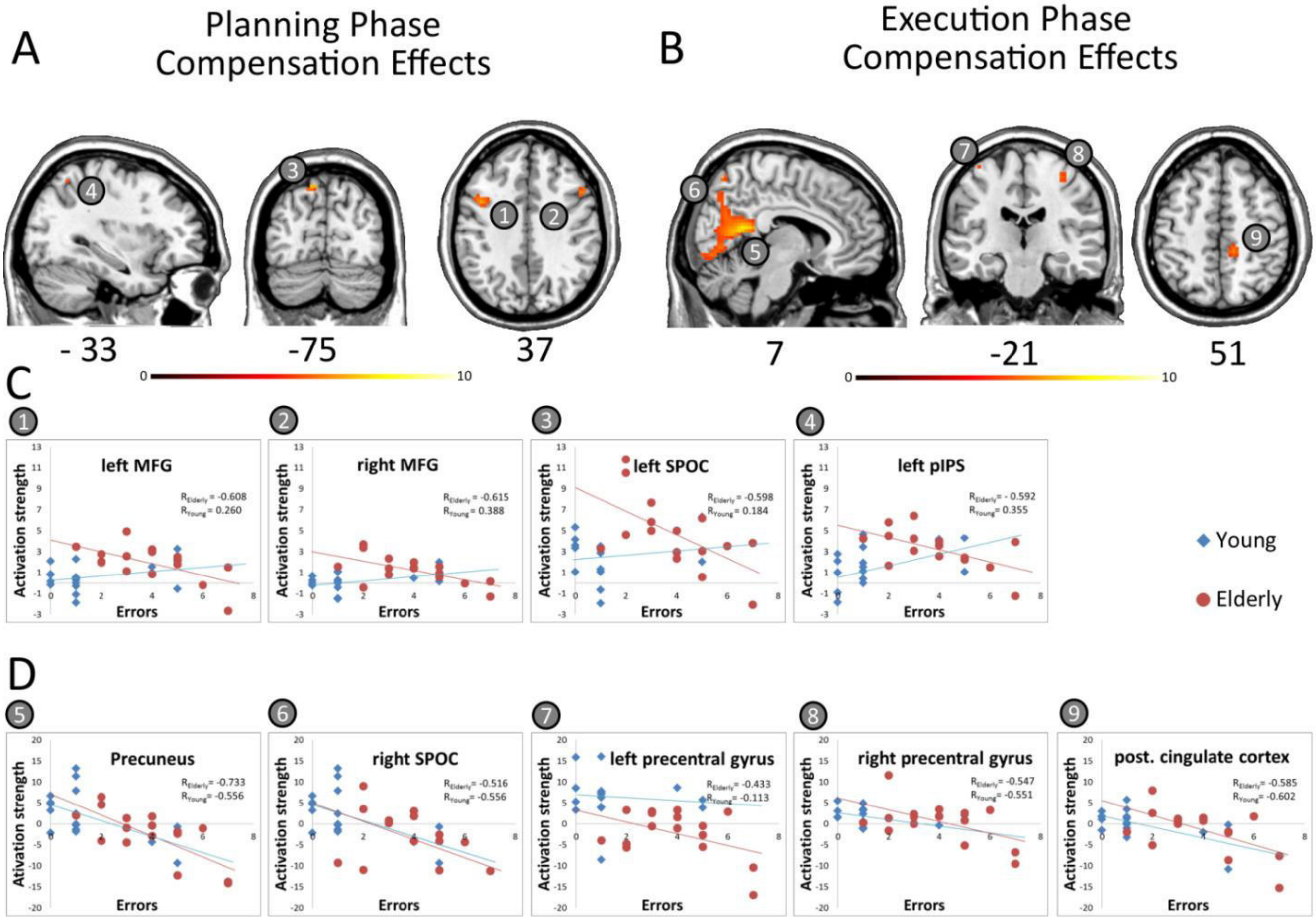

Figure 5: Results of the multiple regression analysis testing for compensatory effects in the elderly. **A)** Activation map showing significant negative correlations between the number of errors made and the activation strength during action planning in elderly adults at $p < 0.05$ (FWE corrected). **B)** Activation map showing significant negative correlations between the number of errors made and the activation strength during action execution in elderly adults at $p < 0.05$ (FWE corrected). **C)** The graphics plot the participant's activation strength on the y-axis and the individual errors on the x-axis in red for the elderly and in blue for the young adults. Shown are the correlations between behavior and activation during action planning of the left and right MFG (labeled with number 1 and 2), the left SPOC (number 3) and the posterior part of intraparietal sulcus (number 4) **D)** The graphics plot the participant's activation strength and the individual errors in red for the elderly and in blue for the young adults. Shown are the correlations between behavior and activation during action execution in the precuneus (number 5), the right SPOC (number 6), posterior cingulate cortex (number 9) and the left and right precentral gyrus (number 7 and 8).

Laterality index - Similar left-sided lateralization in both groups

To evaluate possible age related differences in the laterality of activated brain patters, the LI was calculated for each group and frontal, occipital, parietal, temporal and the sensorimotor cortex separately for each condition. The mean LI of both groups and the p–value of the t-test testing significant differences compared to zero are listed in Table 5. Similarly, as it already had been reported in young adults (Brandi et al., 2014), the elderly show a significant left-sided lateralization in most conditions during the planning phase in the frontal, parietal, temporal and sensorimotor cortex. During action executions it is mostly the use conditions, which show a significant left sided lateralization in the frontal, occipital, parietal and temporal cortex. The two sample t-test testing for group differences did reveal a significant difference in lateralization between elderly and young only in the condition bar use in the occipital lobe during action planning with a stronger left-sided lateralization in the young adults (p = 0.030) and bar use in the sensorimotor cortex during action execution with a stronger left-sided lateralization in the elderly (p = 0.048).

Table 5: The mean LIs for all conditions, lobes and both groups for planning and execution phase including the p-values of the t-test measuring the significance of laterality.

		Frontal Lobule			**Parietal Lobule**			**Temporal Lobule**			**Occipital Lobule**			**Sensorimotor Cortex**		
	Condition	**LI**	**p-value**		**LI**	**p-value**		**LI**	**p-value**		**LI**	**p-value**		**LI**	**p-value**	
Planning Phase																
Elderly	Tool Use	0.390	0.001	*	0.557	0.000	*	0.318	0.007	*	0.039	0.744		0.308	0.038	*
	Tool Transport	0.508	0.000	*	0.622	0.000	*	0.480	0.000	*	0.133	0.232		0.533	0.000	*
	Bar Use	0.246	0.037	*	0.459	0.000	*	0.124	0.283		-0.028	0.820		0.127	0.364	
	Bar Transport	0.406	0.000	*	0.371	0.006	*	0.296	0.012	*	0.012	0.914		0.173	0.276	
Young	Tool Use	0.331	0.002	*	0.562	0.000	*	0.370	0.003	*	0.095	0.434		0.585	0.000	*
	Tool Transport	0.454	0.000	*	0.436	0.003	*	0.297	0.036	*	0.056	0.653		0.440	0.004	*
	Bar Use	0.184	0.104		0.333	0.000	*	0.259	0.045	*	0.277	0.004	*	0.399	0.003	*
	Bar Transport	0.271	0.008	*	0.322	0.014	*	0.236	0.058		0.070	0.613		0.340	0.013	*
Execution Phase																
Elderly	Tool Use	0.242	0.017	*	0.360	0.033	*	0.546	0.000	*	0.476	0.005	*	0.125	0.455	
	Tool Transport	0.010	0.940		0.331	0.056		0.236	0.152		0.243	0.156		0.249	0.093	
	Bar Use	0.100	0.400		0.410	0.011	*	0.443	0.001	*	0.364	0.004	*	0.223	0.185	
	Bar Transport	-0.044	0.767		0.237	0.210		0.180	0.287		0.224	0.140		-0.101	0.526	
Young	Tool Use	0.472	0.000	*	0.561	0.000	*	0.602	0.000	*	0.691	0.000	*	-0.103	0.464	
	Tool Transport	0.139	0.138		0.357	0.033	*	0.330	0.051		0.287	0.073		-0.117	0.322	
	Bar Use	0.318	0.003	*	0.480	0.000	*	0.499	0.000	*	0.519	0.000	*	-0.190	0.084	
	Bar Transport	-0.006	0.948		0.176	0.218		0.058	0.730		-0.046	0.767		-0.362	0.000	*

Indicated with a star (*) are significant p-values.

Discussion

Our current study aimed to compare the neural network of young and elderly adults which is responsible for processing the planning and execution of complex object manipulations and investigate possible underlying mechanisms. The neural basis of tool use has been studied before with the help of the "Tool-Carousel" in young individuals (Brandi et al., 2014) and here we are able to show consistencies and alterations of this basic network in elderly adults to expand the understanding of neural processes in healthy aging but also to provide a close link to the neuroanatomical correlates of patients suffering from apraxia.

Overall our results show that the main activation pattern for tool manipulations compared to manipulations of neutral objects is stable across age and includes the same activations in the IPL and ventral stream areas during action planning and additional activations in the SPL, PMv and insula cortex during action execution. Additionally, it can be stated that this network is strongly left lateralized in both age groups. Therefore the loss in lateralization as it is described in the HAROLD model (hemispheric asymmetry reduction in older adults) in the domains of episodic memory, working memory, perception and inhibitory control (Cabeza, 2002) cannot be directly applied to the process of tool use. Behaviorally we found no overall differences in the reaction time or the duration of movement between groups, showing that aging is not necessarily associated with slower task performances (Cicerale et al., 2014) and that the experimental timing was suitable for both groups.

Next to these similarities we also found differences between groups on a structural, behavioral and neural level. As it has been shown in existing studies, we furthermore find a decreased grey matter volume and increased CSF volume in the elderly (Good et al., 2001; Seidler et al., 2010). Behaviorally, the strongest difference between groups can be found in the amount of errors made. Even though the elderly were able to perform the task in the given timeframe, they showed greater difficulties in performing the tasks correctly. They mainly showed problems in switching between conditions and performing the task as it is cued and in executing precise and accurate grip movements. Decreased task performance of the elderly has been reported before (Spreng et al., 2010) and is also known for different aspects of grasping actions (Diermayr et al., 2011; Noble et al., 2011; Vieluf et al., 2012). On the neural level we showed two major age-related findings: (i) The activation strength of several brain areas differ between the age groups for all conditions and between action phases (ii) the elderly show compensation effects in both planning and execution phase.

Age related differences in activation strength during planning and executing actions

The difference in activation strength is seen both in action planning and execution as a result of the group comparison, but interestingly with a different direction in both phases. During action planning the elderly recruit a wider network including several brain areas which are relevant for actions with objects including clusters in the IPL, SMG, SPOC, MTG, LOC and also inferior frontal areas (PMv). Interestingly, looking at overall differences between groups in this comparison, we see a more bilateral activation pattern as it is described in the HAROLD model (Cabeza, 2002). This leads to the conclusion that task specific neural processes related to tool manipulations retain their laterality in elderly, but that the overall level of activation strength during planning of actions is bilaterally increased in aging.

To our knowledge, not many age-related neuroimaging studies separated planning phases (without the movement) and execution phases (including the movement) and looked at both phases individually. Berchicci et al. (2012) conducted an EEG study on movement planning and also found prefrontal hyperactivity in elderly. Additionally, studies on motor imagery show an age-related increase in the overall brain activity (Saimpont et al., 2013). Interestingly, elderly adults recruit less resources during action execution compared to young, which is surprising considering several studies which find increased activation during motor acts in the elderly (Mattay et al., 2002; Heuninckx et al., 2008; Ward et al., 2008; Seidler et al., 2010). In general, decreased activation strength is no new finding in age studies and had been reported before in other cognitive domains (Spreng et al., 2010) but not for the processes of monitoring action execution. One possible reason for this discrepancy with the existing literature could be that previous studies looking at difference in motor tasks do not separate between both action phases and analyze simpler actions. To our understanding, the planning and execution of actions recruit similar brain areas, but process different elements of an action. During action planning the object and goal has to be recognized and the motor plan has to be created and prepared, while during the execution phase this plan is actually carried out, monitored and controlled to achieve a goal-directed movement. As measured in the control analysis comparing the activation strength of both phases within the two groups, we see that elderly show reduced activations during action execution. We hypothesize that in the elderly the neural recruitment of relevant resources is strongly shifted to the planning phase in order to prepare the execution of complex actions. This indicates that the planning phase of an action is highly important for elderly adults to perform object manipulations and it is therefore very interesting, that similar areas which have an increased activation also show a relation to behavioral scores, as it will be discussed in the following section.

Compensatory effects in the elderly during action planning and execution

The often found increase of activations in the elderly has been explained by a compensatory effect in both the cognitive (Reuter-Lorenz et al., 2000; Vallesi et al., 2011) and the motor domain (Ward, 2006; Heuninckx et al., 2008) and results in a positive relation between good performance and increased activity. We also find this outcome in our study selectively for elderly during action planning. Here the left pIPS, SPOC and both left and right MFG/IFG all indicate a compensatory effect and also show close proximity and overlap with those regions with increased brain activations mentioned earlier. Especially bilateral compensatory effects in the frontal lobe have been reported before in perception, executive functions (Spreng et al., 2010) but also in motor tasks (Heuninckx et al., 2008) and its activation seems to have a strong influence on the performance of the elderly. An increased activity associated with fewer errors is also seen in the SPOC, which is known to be a brain region related to reaching and grasping actions (Gallivan et al., 2009) which often show age-related changes in the elderly (Gilles and Wing, 2003; Diermayr et al., 2008; Noble et al., 2011; Vieluf et al., 2012). It seems that the MFG, IFG and SPOC are crucial brain areas with compensatory abilities that have a strong relation to behavioral performance in elderly and might have a key role in aging-related cognitive and movement impairments.

Fine Dedifferentiation effects in elderly adults

Dedifferentiation is mainly characterized by decreased distinctiveness in brain activations for tasks in which young adults show selective activations in specific brain areas. It is hypothesized that different neural processes rely on the same structures in elderly while they are differentiated in the neural activation patterns in young adults (Li et al., 2001; Park et al., 2004; Carp et al., 2011). We tested this hypothesis by looking at the interactions of the two experimental factors object and task with the factor age to see if the activation differences between conditions are significantly lower in the elderly. The whole brain analysis showed no significant interaction effects and we can speculate that in our case the concept dedifferentiation is of minor importance concerning object manipulations. Only a more sensitive analysis revealed neural dedifferentiation for the factor object in the superior parietal lobe which is a region relevant for reaching and grasping movements as well as the online control of object manipulations (Karnath and Perenin, 2005; Heim et al., 2012; Brandi et al., 2014). Object-identity related dedifferentiation in SPL during action planning might lead to a limited ability in elderly to form object specific reaching and grasping plans which might lead to an altered grasping behavior (Cicerale et al., 2014).

Taken together we see that neural age-related differences during object manipulations include a difference in the general activation strength, with a higher level of recruitment in action planning and lower activations during the execution of actions in the elderly. Age-related compensatory mechanisms are present and especially structures of the inferior frontal lobe and the superior parietal occipital complex show increased activations during action planning and also a correlation between performance and activation strength. It can be speculated, that atrophy in these brain areas or other severe incidences like stroke, could have a severe impact on behavior due to a decreased ability to compensate for age-related deficits in those individuals.

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4 The Tool in the Brain: Apraxia in ADL. Behavioral and Neurological Correlates of Apraxia in Daily Living

The conceptual understanding, sequencing and spatio-temporal processing of tool use are represented by characteristic brain networks which are affected by lesions in patients with left brain damage.

A literature review of the behavioral deficits and neural basis in activities of daily living (ADL) in patients with apraxia and action disorganization syndrome titled "The tool in the brain: apraxia in ADL. Behavioral and neurological correlates of apraxia in daily living.", written by Marta Bieńkiewicz, Marie-Luise Brandi, Georg Goldenberg, Charmayne Hughes and Joachim Hermsdörfer, was published in the journal Frontiers in psychology in 2014. The review covers behavioral studies on patients with brain damage and differentiates three aspects of actions and activities which are impaired in brain damaged patients. The impairments include the conceptual understanding of tool use, the sequencing of multi-step actions and the spatio-temporal organization of tool use. The neural basis of these aspects in healthy individuals and the lesions associated with erroneous tool use actions in patients are summarized as well in this review. The latter aspect was reviewed and written by the author of this thesis and is therefore of main interest in the later discussion.

Contributions:

The author of this thesis is a coauthor of the review. M.B., M.L.B., G.G., C.H. and J.H. formulated the concept and focus of the review. M.B., M.L.B., G.G., and J.H. wrote the review.

M.L.B. wrote part of the review including the sections "The Neural Basis of ADL", "Healthy Adult Studies" "Action Sequencing" "Conceptual Knowledge of Tool Use", "Spatiotemporal Organization of Movements", "Summary of the functional Imaging Healthy Adults section" and "Lesion Analysis in Patients with Brain Damage".

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The tool in the brain: apraxia in ADL. Behavioral and neurological correlates of apraxia in daily living

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Humans differ from other animals in the way they can skilfully and precisely operate or invent tools to facilitate their everyday life. Tools have dominated our home, travel and work environment, becoming an integral step for our motor skills development. What happens when the part of the brain responsible for tool use is damaged in our adult life due to a cerebrovascular accident? How does daily life change when we lose the previously mastered ability to make use of the objects around us? How do patients suffering from compromised tool use cope with food preparation, personal hygiene, grooming, housework, or use of home appliances? In this literature review we present a state of the art for single and multiple tool use research, with a focus on the impact that apraxia (impaired ability to perform tool-based actions) and action disorganization syndrome (ADS; impaired ability to carry out multi-step actions) have on activities of daily living (ADL). Firstly, we summarize the behavioral studies investigating the impact of apraxia and other comorbidity syndromes, such as neglect or visual extinction, on ADL. We discuss the hallmarks of the compromised tool use in terms of the sequencing of action steps, conceptual errors committed, spatial motor control, and temporal organization of the movement. In addition, we present an up-to-date overview of the neuroimaging and lesion analyses studies that provide an insight into neural correlates of tool use in the human brain and functional changes in the neural organization following a stroke, in the context of ADL. Finally we discuss the current practice in neurorehabilitation of ADL in apraxia and ADS aiming at increasing patients' independence.

Keywords: apraxia, action disorganization syndrome (ADS), activities of daily living (ADL), tool use, cerebrovascular accident (CVA), quality of life, stroke patients

INTRODUCTION

Left brain damage caused by ischemic or hemorrhagic stroke is the most frequent neurological correlate of apraxia (Goldenberg, 2013). However, features of apraxic behavior can be also observed in numerous other neurodegenerative disorders (such as Parkinson's disease, Alzheimer's disease or posterior cortical atrophy; Bohlhalter and Osiurak, 2013) or occur as an effect of anoxia (Sirigu et al., 1995) and herpes encephalitis (Sirigu et al., 1991). Apraxic behavior in tool use is primarily attributed to the impaired or lost access to the tool related knowledge, concepts of use and problem solving (Goldenberg, 2013). Patients frequently show compromised ability to carry on everyday activities and often show action disturbances leading to safety hazards after dismissal from hospital units (Hanna-Pladdy et al., 2003). Such slips might involve attempts to use a knife in a wrong orientation to cut a slice of bread, bite a toothbrush instead of applying a brushing movement inside the mouth, toy with boiled water or tear the teabag to make a cup of tea. Problems with sequential tasks, concepts of use and smooth execution on the spatiotemporal level cannot be attributed to the deficit of function on the ipsilesional hand of patients. Patients are not able to perform the task even with the contralesional limb which might have preserved motor functionality.

The purpose of this review is to present a comprehensive summary of the research investigating apraxia syndrome following a cerebrovascular accident (CVA) and its influence on independence during activities of daily living (ADL). First, we provide a systematic overview of the behavioral research investigating impact of apraxia on three basic areas of object and action related abilities: sequencing of action, tool and gesture knowledge and spatiotemporal features of the movement, in the context of basic needs of independence. A particular focus is placed on research investigating the influence of those functions on ADL such as food preparation, personal hygiene, grooming and use of household appliances, or housework tools. The second part of this review is dedicated to the cut-edge neuroimaging research, demonstrating how multi-faceted the neural basis of tool use and ADL is as well as the current state of the art.

DEFINITION OF APRAXIA

The most commonly used definition of apraxia was coined by Rothi and Heilman (1997) which states: "Apraxia is a neurological disorder of skilled movement that is not explained by deficits of elemental motor or sensory system." In other words, apraxia is considered as being independent from other stroke comorbidity symptoms such as hemiplegia (loss of proprioception and motor control over limb on one side) or visual deficits such as hemianopia or neglect. However, as discussed in the penultimate section of this review, comorbidity symptoms occurring as a consequence of CVA contribute to overall ADL in a substantial manner and might even be difficult to disentangle with apraxic features. Until recently, a vast number of clinicians and researchers used the original postulation by Hugo Liepmann (a German pioneer in apraxia research) and distinguished three separate types of apraxia: ideational, ideo-kinetic (or ideomotor), and limb-kinetic (Goldenberg, 2003, 2013). Ideational apraxia refers to an inability to use familiar tools that were previously handled in an effective and purposeful manner; choosing the right object for a required action goal and carrying out multi-step naturalistic action (Goldenberg, 2013). The second category, namely ideo-kinetic apraxia, described compromised ability to pantomime actions; mimicking tool use without holding object, and/or difficulty with gesture production. In the literature, gesture production is usually divided into transitive and intransitive acts. Transitive gestures relate to object use, showing how one would use an object, whereas intransitive gestures refer to non-tool related movements, such as waving goodbye or giving someone the thumbs up. Thus, patients were reported to be unable to produce gestures that would mirror the relevant semantic representation they wished to convey (Hogrefe et al., 2012). Interestingly, even if apraxic patients attempt to operate the tool in a goal-directed fashion, they might do it in a spatiotemporally erratic manner (Poizner et al., 1995; Hermsdörfer et al., 1999; Laimgruber et al., 2005; Randerath et al., 2010). These errors are reminiscent of "limb-kinetic apraxia," which was introduced to describe hesitation and disrupted smoothness of the movement when operating tools (both multiple and single) or disruptions of fine and precise movements, but affects only the limb opposite to the lesion (Heilman et al., 2000). To summarize, the main cognitive domains affected by apraxia comprise of the use of tools (multiple and single) and gesture production.

DISAMBIGUATION AND COMMON GROUND BETWEEN APRAXIA AND ACTION DISORGANIZATION SYNDROME

As previously mentioned, apraxia, since the work of Hugo Liepmann, is usually linked to left brain damage (Goldenberg, 2013). Original descriptions (i.e., by Pick) of ideational apraxia were inclusive of disturbances in multi-step action performance (Goldenberg, 2013). A plethora of research demonstrates that patients suffering from right brain lesions also show disruption in terms of naturalistic action organization, referred to as action disorganization syndrome (ADS; Schwartz et al., 1999; Forde et al., 2004; Hartmann et al., 2005). ADS is a term used to describe compromised ability to sequence fixed chains of actions in an appropriate manner in relation to any naturalistic action (Humphreys and Forde, 1998). However, the differentiation between ADS and apraxia (especially ideational) is disputed. Therefore apraxia and ADS can be described under the umbrella term "apraxia and action disorganization syndrome" (AADS; Humphreys and Forde, 1998). Therefore in this review we incorporate studies investigating ADS, especially since patients with left brain damage also show difficulties with sequencing of action subtasks (Goldenberg, 2013). Probably the most puzzling element in the investigation of AADS is the lack of consistent evidence as to which brain lesions are related to the designated action problems.

EPIDEMIOLOGY

The epidemiology of AADS was most recently reported by Bickerton et al. (2012). Approximately 46% of patients, who suffered from a first CVA were identified as symptomatic of AADS (within 6 weeks from CVA, 231 participants) based on the neuropsychological assessment (Birmingham Cognitive Screen). The criterion was impairment on one of four praxis tasks: pantomime, tool use during multi-step actions, gesture recognition or imitation. Furthermore, in the same study around 52% of those patients have shown persistent signs of AADS that did not diminish with the course of neurorehabilitation (24% of the initial sample). Previous reports, which solely focused on left hemisphere stroke survivors, estimated a rate of ideo-kinetic apraxia occurrence at approximately 30% (De Renzi, 1989). Donkervoort et al. (2001) had found that around 28% of all CVA survivors in the Dutch rehabilitation centers and 37% of nursing homes, show persistent signs of apraxia and therefore compromised ADL independence. In a later study, Donkervoort et al. (2006) stated that 88% of patients diagnosed clinically, in the acute stage with features of apraxia, were still apraxic 20 weeks post first measurement (100 days after CVA). Importantly, greater improvement over the course of rehabilitation was observed in patients that initially have had more severe deficits, whereas those with mild impairments tended to improve to a (clinically) less significant extent (measured with Barthel Index; Mahoney, 1965). Donkervoort et al. (2006) concluded that apraxia is a persistent impairment and has a negative effect on ADL. In a similar vein, Smania et al. (2006) demonstrated that apraxia is negatively correlated with the ADL independence, based on responses from patients and caregivers. On the contrary, De Renzi (1986) reported that in natural setting apraxic features are less salient due to the contextual cueing. In other words, if a patient in the hospital or lab setting has a difficulty with a simple gesture production, the same individual might still be able to perform the gesture whenever prompted by the environment (for example, to wave goodbye). Environmental information therefore has the potential to provide additional cues to promote selection of an appropriate motor program (Hermsdörfer et al., 2006). Although there is a lot of theoretical evidence supporting this view, there is no scientific ground yet to support this stance.

USE OF ADL SCALES IN AADS

Several scales are commonly used by the clinical professionals for the assessment of ADL independence in neurological patients. Such scales are usually based on self-report or questionnaire (Barthel Index of ADL or Bristol ADL Scale; Mahoney, 1965; Bucks et al., 1996) or observation of action performed during clinical assessment (e.g., E-ADL, TULIA, NE-ADL; Gladman et al., 1993; Graessel et al., 2009; Vanbellingen et al., 2010). Those assessment tools are used not only to aid the clinical diagnosis of patients' impairments, but also, if not primarily, to monitor efficacy of interventions to foster independence in cohort studies or clinical trials for example. Therefore the application of those scales in the clinical setting is common. Moreover, some studies have attempted to predict the speed and extent of patients' recovery based on the overall score. For instance, Barthel Index scores measured within the approximately 3 weeks of CVA were found to be accurate predictors of compromised ADL independence in 6 months post CVA (Nakao et al., 2010). Similarly, a recent study by Bickerton et al. (2012) has noted a correlation between a multi-step action task execution and Barthel Index. Nonetheless, the assessment scales and neuropsychological batteries do not capture fully the apraxic problems patients might encounter during their daily life. Hence, relevant behavioral studies were selected for the purpose of this review to shed a light on the spectrum of difficulties that can be observed in those patients during ADL.

BEHAVIORAL STUDIES

Most of the behavioral studies investigating apraxia following CVA focus on behavioral data with qualitative error categorization (Foundas et al., 1995; Schwartz et al., 1999). As such, the most predominant methodology includes video recordings of patients' performance and then arbitrary classification of action errors. Setting aside the original descriptions and attempts to classify apraxia, for the purpose of this review, we can distinguish three major dimensions of action performance where apraxic features can be identified. The first one refers to sequencing problems during ADL and links to the description of ADS, compromised ability to perform subsequent actions in the correct temporal order with spatial constraints, in order to achieve an action goal (pack a lunchbox; Humphreys and Forde, 1998). For example, if one attempts to make a cup of tea, common error would involve putting cold water, not previously heated in a kettle, straight into the mug (omission error). The second area that will be discussed in this review refers to conceptual errors that might lead to the selection of the inappropriate motor plan. For example, with reference to the previously used example of tea making, one can use coffee grains instead of tea bags (substitution error; Goldenberg, 2013). In a similar fashion, communicative gestures might be misused or misunderstood. Finally, other mistakes might occur on the spatiotemporal dimension, even if the right tool is selected for action. The handling of the tool might not be adequate in terms of movement orientation, applied speed of the movement or grasp (Laimgruber et al., 2005; Randerath et al., 2010). For example, an apraxic individual might be unable to open the kettle lid during an attempt to make a cup of tea.

SEQUENCING PROBLEMS

Daily activities rarely rely on single tool actions which require only one tool-object interaction. The majority of the actions we perform involve multistep actions leading to an action goal. The achievement of the action is comprised of the different action subgoals, constituting to chains of different activities (Goldenberg, 2013). To perform a coherent action (i.e., make a sandwich), different steps need to be organized within certain constraints of time and space (Goldenberg et al., 2001). For example, even if the individual action step is performed in a correct manner, the temporal position in the sequence chain might be out of place, in effect, leading to failure in achieving the action goal. Referring again to making a cup of tea, a person might put the kettle on, having not previously put the water inside or using another example: brush their teeth having not put the toothpaste on. Usually those errors refer to the temporal organization of the action sequence, but are not related to the personal context of actions. The overall execution of specific sequences during ADL varies interpersonally and relies on personal abilities and preferences (Land, 2006; Goldenberg, 2013; Hughes et al., 2013). Therefore, the scientific investigation of ADLs is inherently burdened with a high level of complexity of analysis and must permit a certain level of homogeneity between examined subjects. For example, healthy adults might perform an action of making a cup of tea in a variety of ways and preferences (i.e., time of the tea bag being dipped in the mug, number of sugar cubes inside) with some other sequences being constant (i.e., heating the water in a kettle before pouring it in the mug), in order to achieve an action goal (make a cup of tea). Hence certain sequences are always fixed, whereas others show a high level of inter-subject variability (Hughes et al., 2013). If the error occurs in the fixed chain of sequences, it leads to the failure to achieve the task goal and is not recoverable until the next attempt (pouring cold water into the mug with teabag inside). If however the error occurs in the "not-fixed" chain of activities, it might be recoverable.

The most frequent sequencing error in terms of action performance is the omission error, which refers to omitting a step before another one (Schwartz et al., 1999). For example, a patient might put a piece of paper into an arch file before using the hole-punch. In addition, more general sequence errors are when the patients perform something in the wrong order. Such an instance would be putting or adding an extra sequence or ingredient (addition) that is not needed or that is repeated (perseveration error; Rumiati et al., 2001). In another scenario, a subtask might be performed too early in the chain of sequences (anticipation error). An example of sequence addition error would be folding a piece of paper before putting it into the arch file in a document filing task. Another type of addition, based on the use of additional objects or ingredients (in food related tasks) would be (using the previously mentioned example) putting a piece of scotch tape on the top of the paper. In sum, CVA subjects might engage in sparse subtasks that are not relevant in the context of achieving the action goal. In the same task, a perseveration error would describe repetition of the previously accomplished subtask, such as making more punch holes than necessary. There is a plethora of research that has attempted to capture the most common error occurrences in naturalistic action performance with different types of error patterns. However, the results show some incongruence between the terminology used and the classification of errors (see Goldenberg, 2013, Chap. 9, for review on this issue). Previously mentioned omission errors reach an approximate ratio of 40–50% for all action errors (Schwartz et al., 1999; Bickerton et al., 2007). Importantly, the tendency to skip a step that is necessary for achieving the action goal seems to be linked to the level of familiarity with the object. Novel object, which are not familiar to patients seem to elicit the highest number of those errors (Bickerton et al., 2007). Other authors also point out the prevalence of these types of action errors, but they use different terminology to describe it, namely sequence error

(De Renzi and Lucchelli, 1988) or action anticipation (Rumiati et al., 2001). **Table 1** presents an overview of research describing the sequencing errors related to the ADL in stroke survivors studies.

As reported in **Table 1**, there is a substantial body of research attempting to capture problems with sequencing of ADL in CVA patients. Different classifications are proposed by many research groups, but not all of them fit to every ADL, due to the variation in the fixed or not fixed action chains. However, most authors agree that problems with the organization of particular subtasks should be referred to as sequence errors, with subclasses, such as addition errors or anticipation, or without (De Renzi and Lucchelli, 1988; Schwartz et al., 1999; Rumiati et al., 2001; Goldenberg, 2013). In the seminal study by Foundas et al. (1995) conducted on 10 patients with unilateral left hemisphere CVA no error classification was used. Authors observed the lunchtime behavior (via video taping) on the hospital ward and divided the overall meal organization into three phases: preparatory, eating and clean up. Only 20% of CVA patients proceeded with all three phases of the meal and only 40% demonstrated preparatory behavior. In comparison to all healthy age-matched controls engaged in preparation of the meal, and 80% in the clean-up phase. In addition, patients used fewer tools (cutlery) than controls and shown different pattern of food consumption (consuming one ingredient in a sequential fashion or drink a glass of refreshment at once) in comparison to controls (who preferred to mix different ingredients and take small sips of drink).

CONCEPTS OF USE AND GESTURE KNOWLEDGE

On the cognitive level, the knowledge about concepts of use can be referred to as both functional knowledge (Sirigu et al., 1995) and the ability for mechanical problem solving (Goldenberg and Hagmann, 1998; Osiurak et al., 2009). Functional knowledge specifies the typical purpose, recipients, and manner of using distinct types of tools (Sirigu et al., 1991; Hodges et al., 2000; Rumiati et al., 2001). This type of expertise embraces global motor concepts, inclusive of the recipient of the action, relevant manipulation, and tool selection for the desired action goal (Goldenberg, 2013). For example, a hammer can be used to put a nail into a block of wood through forceful strokes. The knowledge necessary to achieve this goal includes: choosing the right tool from the toolbox (hammer); knowing how to position the nail in the block of wood and knowing what

Table 1 | Summary of studies on sequencing errors related to the ADL in AADS.

Source	Participants	Task	Main results
Bickerton et al. (2007)	ADS patient ($N = 1$); patients with brain lesions ($N = 4$); age- and sex matched controls ($N = 5$)	Making a cup of tea/coffee/toast/sandwich, wrapping a gift, write and post a letter, packing a lunchbox, putting an article from a magazine into a file	ADS patient made more omission steps with unfamiliar than familiar objects compared to controls (2 and 0.5 errors, respectively)
Bickerton et al. (2012)	RBD and LBD ($N = 635$), age- and sex matched controls ($N = 100$)	Mounting a torch and switching on light (MOT task)	No differences between LBD and RBD in MOT score, low but consistent correlation between MOT and Barthel Index ($r = 0.29$) and Nottingham Extended ADL scale ($r = 0.32$)
Buxbaum (1998)	Patients with LBD ($N = 16$)	Wrapping a gift, making toast, packing a lunchbox	Ratio of errors: omissions (44%), sequence errors (27%)
Humphreys and Forde (1998)	ADS patient ($N = 2$)	Wrapping a gift, posting a letter, making toast/sandwich/cup of coffee, preparing cereal, tooth brushing, shaving, painting wood	Omissions (24%), sequence errors (40%); patients better with shorter than with longer tasks
Schwartz et al. (1999)	Patients with RBD ($N = 30$)	Wrapping a gift, making toast, packing a lunchbox	Omissions (47%), sequence errors (19%)
Sunderland et al. (2006)	Patients with right and left hemisphere stroke ($N = 8$), five RBD, four LBD	Dressing	76% LBD demonstrated a planning problem (dressing first the non-paretic arm), RBD attentional and spatial problems (e.g., finding sleeve opening), 16% of RBD did not push sleeve over the paretic elbow

LBD – left brain damage, RBD – right brain damage.

movement to apply. There is, however, controversy whether the kinematics of actions and the formation of adequate hand postures are stored in a separate compartment of semantic memory as "manipulation knowledge" or are derived from structural properties of tools by mechanical problem solving (Goldenberg and Spatt, 2009; Osiurak et al., 2009; Kalénine et al., 2010). Patients with loss of functional tool use knowledge may be able to infer the function of the object from their structure (Goldenberg, 2009). In the modern type of devices however, such as technically advanced coffee machines with capsules, patients are not able to deduce (use mechanical problem solving) how to operate the device based on its physical structure. Therefore those types of the devices (such as tablets or smart TV) might be almost impossible to operate for apraxic individuals (Hartmann et al., 2005).

In principle, ADL can be divided into multiple tool use and single tool use actions (Goldenberg, 1996, 2013). For example, making a cup of tea would be an example of complex and multiple tool based action. On the contrary, fixing a loose screw would be based on single tool use, namely a screwdriver. One of the common errors noted in the literature is mislocation or misplacing of the tool (De Renzi and Lucchelli, 1988; Schwartz et al., 1999) or spatial error as described by Humphreys and Forde (1998). De Renzi and Lucchelli (1988) tested 20 patients in the tool use and pantomime paradigm. Among other errors, author's differentiated mislocation as appropriate action carried out in the spatially inadequate place. For instance, patients were able to strike a match, but tried to lit the wrong side of the candle. Misuse of the tool has also been identified by De Renzi and Lucchelli (1988) and Rumiati et al. (2001). Misuse can be defined as use of object in conceptually inappropriate way, i.e., rubbing candle onto the table, or handling object by the wrong end (De Renzi and Lucchelli, 1988). All of the error classifications mentioned refer to the impaired ability to handle the tool in a relevant manner (i.e., also include uncomfortable grasp of the tool). Other research also reports wrong object selection (Humphreys and Forde, 1998; Goldenberg, 2009) or object substitution (Schwartz et al., 1999). Humphreys and Forde (1998) tested two patients with features of AADS on ten ADL tasks (see **Table 1**). In the tea making task, one of the patient demonstrated repetitive errors of pouring milk into the teapot rather the mug. Authors referred to it as semantic error, specific for object selection. Schwartz et al. (1999) tested 30 patients with right hemisphere lesions following CVA on three ADL tasks (making a toast, wrapping present, and packing lunchbox). Object substitution was defined as correct movement performed with wrong object, i.e., putting a slice of bread on a hot plate instead inside the toaster. In addition, misestimation errors, i.e., too little or too much of one ingredient, were introduced in studies looking into food related behavior (Foundas et al., 1995). For example, patients were reported to put too little food on their plate and fork during daily lunchtime behavior or making a toast (Foundas et al., 1995; Schwartz et al., 1999). Importantly, the differences within classification of the errors are arbitrary and do not have a consequence on the overall understanding of the difficulties patients exhibit with ADL. Patients might choose the wrong tool for an action, for example, picking up a screwdriver to connect two sheets of paper together. In many occasions the difficulties with access to the adequate motor concepts do not manifest themselves directly but are observable as perplexity or toying behavior. Those errors are not explicitly categorized separately by all researchers (e.g., Schwartz et al., 1999). Perplexity refers to pauses in movement, or inefficient manipulation. For example, the patient might pick up objects and then set them back on the work surface and cease further trials to accomplish the task goal. Toying, on the other hand describes handling an object in a non-purposeful fashion. One measure that can capture those behaviors, aside from video scoring of conceptual errors committed by patient, is movement time for the task completion.

SPATIOTEMPORAL FEATURES OF APRAXIA

A seminal study by Foundas et al. (1995) on meal preparation, has revealed that left brain damaged patients were less successful in the overall organization of the preparation of meals and that the "correct tool actions" measure significantly correlated with the apraxia score (Florida Apraxia Battery, Rothi et al., 1992). The overall time difference between patients (slightly prolonged) and healthy controls was however not statistically significant. Spatiotemporal errors of movement execution have been documented mostly during pantomime of tool us but have also been found during real tool use (Hermsdörfer et al., 2006). Spatiotemporal errors in the task performance can have a discrete demonstration when the individual is performing an action in a kinematically incongruent manner, which might or might not be observable with the naked eye even for a non-expert viewer. Poizner et al. (1995) and Clark et al. (1994) have demonstrated that apraxic patients with left brain damage suffer from impaired joint coordination and imprecise plane of motion, along with trajectory shape in a bread slicing task. In addition, impaired coupling between the hand speed and trajectory shape was identified. However, it remains open whether these kinematic irregularities reflect deficits of motor-coordination directly or are due to slow and hesitating movement execution due to conceptual problems with planning the action (Hermsdörfer et al., 2006). In other words, impaired movement on the spatiotemporal dimension might be a reflection of compromised movement planning, but not be a feature of limb apraxia. In a seminal study by Laimgruber et al. (2005) left brain damaged patients were found to demonstrate a prolonged adjustment phase before grasping a glass of water, whereas right brain damaged patients showed a decreased velocity of the movement. Speed deficits were also found in the sawing tasks in left brain patients in comparison to age-matched controls (Hermsdörfer et al., 2006). Other variables such as prolonged reaction times and reduced amplitude of the movement were reported for the hammering and scooping movement actions in left brain damaged patients (Hermsdörfer et al., 2006, 2012). Deficits of spatiotemporal aspects of movement execution may be directly or indirectly related to apraxia as indicated above, but also may be indirectly related to spatial deficits such as neglect or they may also be independent consequences of damage to the motor-dominant hemisphere (Hermsdörfer et al., 2012). Randerath et al. (2010) has found that left brain damage patients show impairment in the grasping movements during single tool use. In comparison to healthy age-matched controls, patients demonstrated significantly higher percentage of non-functional grasps of the tools' handles. The impaired grasp was predominately followed by erratic demonstration of the tool use. In the real life scenario, those spatiotemporal deficits might result in mishandling of the object, leading to safety hazards, or frustration (Hanna-Pladdy et al., 2003). In the next section we will present an overview of the neural underpinnings of ADL and apraxia, which will shed more light on the complex organization of human tool use.

THE NEURAL BASIS OF ADL

This section of the review is organized in a similar fashion to the behavioral part, with division of the studies to the sequencing of subgoals of ADL, then conceptual understanding and finally spatiotemporal features of ADL. To provide an insight into the neural correlates of ADL and apraxia, we present neuroimaging studies with healthy subjects followed by lesion analyses with apraxic patients.

HEALTHY ADULT STUDIES

We aim to discuss the neural basis of ADL by including functional neuroimaging studies on viewing, understanding, imagining, pantomiming and executing ADL and single tool use in healthy adults. Furthermore only studies on sequencing actions, tool knowledge and the spatiotemporal features of actions with tools are summarized and visualized here. For the visualization of the neural correlates of these three aspects of ADL, we used the GingerALE toolbox (Eickhoff et al., 2009, 2012) for conducting a meta-analysis. The relevant peak coordinates (in Talairach space) from whole brain analysis were entered separately for the three aspects of ADL. The main aim of this analysis was to provide a descriptive visualization of the activation patterns found in the relevant studies. Therefore a relatively low threshold ($p < 0.05$ FDR corrected) was used to create the ALE images (Laird et al., 2005). The toolbox Mango (Designed and developed by Jack L. Lancaster and Michael J. Martinez) was used to map these thresholded ALE images of all three categories on a rendered brain and to locate the visualized brain areas.

ACTION SEQUENCING

As described previously, patients suffering from AADS show difficulties with sequencing multi-step actions and single tool use. The neural underpinnings of action sequencing in ADL are not yet fully understood. Only a few studies have so far investigated brain regions relevant for sequencing sub-actions of ADL. The most seminal studies in the area were conducted by Schubotz et al. (2012) and Zacks et al. (2001). In these studies subjects had to watch videos depicting different ADL with multiple sequences (for example washing the dishes or ironing a shirt) and had to detect the time borders when each of the sub-actions had commenced. In addition, Weiss et al. (2006) has analyzed the processing of errors in the sequential structure of ADL. Here, subjects had to watch videos of ADL including, for example, pouring a glass of water and drinking it, lighting a candle with matches or affixing a stamp on a letter. These videos were either correct or included errors in the order of sub-actions, which the subjects had to detect. In summary the brain areas relevant for processing the separation and ordering of sequences in ADL cover areas of the frontal, parietal, temporal and occipital cortex. More precisely, these areas were pinpointed to the inferior and middle frontal gyrus, angular gyrus and adjacent precuneus, middle temporal gyrus, fusiform gyrus, and middle occipital gyrus of the left hemisphere. Additional clusters can be seen in the right middle frontal gyrus, middle occipital gyrus, precuneus, inferior and superior temporal gyrus, and fusiform gyrus. The ALE image depicting results from those studies is shown in the **Figure 1** in red.

CONCEPTUAL KNOWLEDGE OF TOOL USE

To get an overview of the neural basis of the conceptual knowledge in the context of ADL and single tool use, we summarized studies investigating how the knowledge of tools and their function is coded in the brain. We included studies comparing correct versus incorrect use of a tool dependent on the context (Mizelle and Wheaton, 2010; Wurm et al., 2012) and studies comparing tool actions of familiar compared to unfamiliar tools (Menz et al., 2010). Exemplary stimuli used in these studies were videos showing actions like punching holes in paper (Wurm et al., 2012) or images and animations of using a hammer (Menz et al., 2010; Mizelle and Wheaton, 2010). In addition, two other studies were included (Manthey et al., 2003; Hoeren et al., 2013), which evaluated both the conceptual understanding of ADL and also the processing of the spatial organization of actions separately. The latter aspect will be discussed in the next paragraph. In the study of Manthey et al. (2003) subjects had to watch videos with ADL and detect object related errors (for example: pour coffee in a glass instead of a cup), or movement errors in the viewed actions (for example: open a bicycle lock but holding the key transverse to the lock). In the Hoeren et al.'s (2013) study subjects were asked to decide, if the object used in an action fits to the context (for example: a cake lifter is used for cake not for a steak in a pan), or if the hand position is correct to perform the known action with the object. In all studies subjects had to show a conceptual understanding of ADL to perform the different tasks. More specifically, the participants had to know the purpose of the actions they saw and the function of the tool used in the actions. Findings from these studies have demonstrated that understanding and tool use function in ADL recruits a wide (mostly left lateralized) network covering frontal, parietal, temporal and occipital centers. Main activation sites were reported on the left hemisphere in the frontal cortex and include inferior, middle and superior frontal gyrus; in the parietal cortex clusters covering anterior to posterior part of the intraparietal area, angular and supramarginal gyrus, and superior parietal lobule activations were reported. Activations in the middle and superior occipital gyrus were found in the occipital cortex. In the temporal lobule, activation patters mainly covered the posterior part of the middle and inferior temporal gyrus and the fusiform gyrus. In the right hemisphere, activation was pinpointed to the middle, superior and inferior frontal gyrus in the superior parietal lobule and anterior part of the intraparietal area, as well as in middle temporal, inferior occipital, and fusiform gyrus. The activation in the right hemisphere is partly homologous to the left areas, but the overall activation pattern comprises less brain areas. A summary of brain network recruitment reported in the mentioned studies is shown in **Figure 1** in blue.

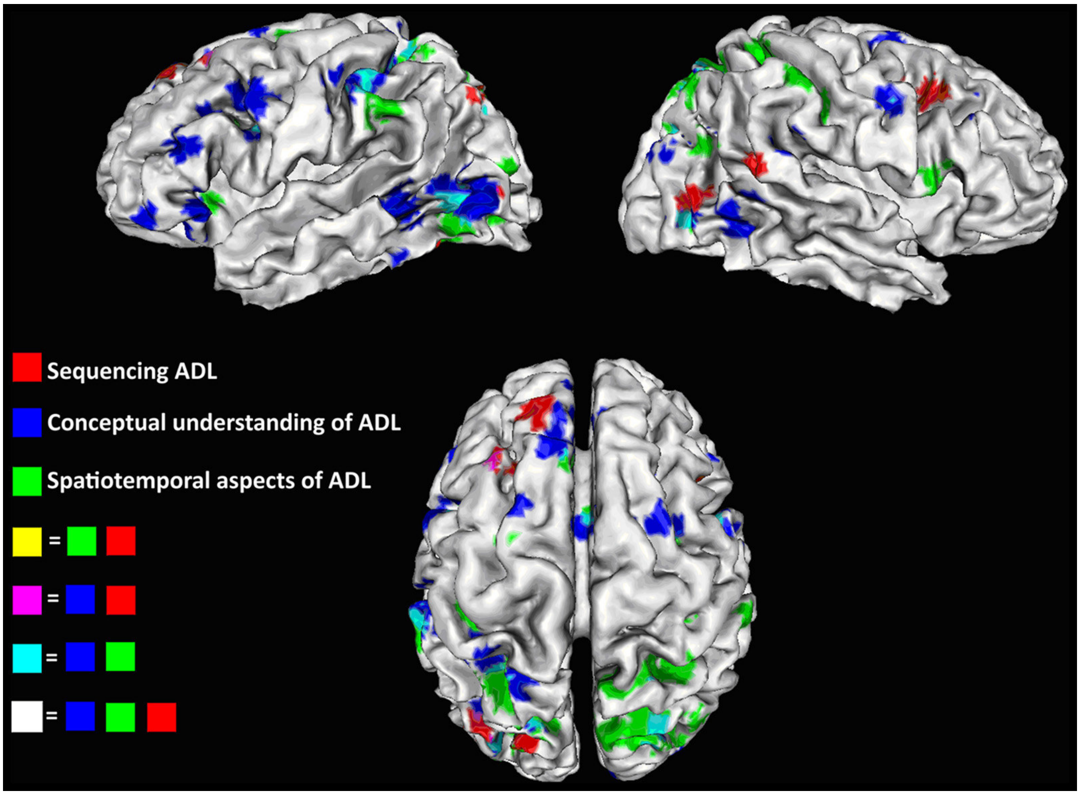

FIGURE 1 | ALE images for studies focusing on action sequencing in red, conceptual understanding of ADL in blue, and spatial orientation of ADL in green; Overlays are depicted in purple (blue + red), light blue (blue + green), and white (all three). Images are produced with the GingerALE toolbox (Eickhoff et al., 2009) and have a threshold of $p < 0.05$ with FDR correction.

SPATIOTEMPORAL ORGANIZATION OF MOVEMENTS

As mentioned in the previous sections of this review, the third component of ADL (following the sequencing of the actions and conceptual knowledge) concerns the tool manipulation necessary to achieve the intended goal and incorporates spatiotemporal features of the movement. This includes grasping the tool in a correct way and moving it accordingly across space. Functional imaging studies have analyzed the brain areas relevant for selecting the correct grip for tool usage during ADL (Valyear and Culham, 2010; Vingerhoets et al., 2010; Hoeren et al., 2013) or the spatial organization of the movement (Manthey et al., 2003; Weiss et al., 2006; Yoon et al., 2012). The neural correlates of this component are more bilateral and mainly include parietal, frontal and occipital areas of both hemispheres. These include the superior and inferior parietal regions, the area close to the posterior part of the intraparietal area and the parieto-occipital sulcus (parieto-occipital junction), premotor cortex and the middle occipital gyrus in both hemispheres. In addition, studies mentioned above have found that the ventral premotor area is relevant in the right hemisphere and the anterior insula in the left. In general, it can be mentioned that most clusters relevant for grip selection and the spatial monitoring of tool use mainly cover regions related to the dorso-dorsal pathway as described by Binkofski and Buxbaum (2012).

SUMMARY OF THE FUNCTIONAL IMAGINING HEALTHY ADULTS SECTION

Investigation of main cortical activation sites of all three aspects of ADL yields the involvement of a wide neural network including frontal, parietal and temporal centers (**Figure 1**). Overlaps were found between the different maps for regions processing conceptual and spatial information of tool use and ADL including frontal clusters in the dorsal and ventral premotor areas, in the anterior cingulate cortex, in the parietal lobe along the intraparietal area, the superior parietal lobule, the supramarginal gyrus, around the parieto-occipital sulcus and in the inferior temporal gyrus of the temporal lobe of the left hemisphere. We have found less overlaps in the right hemisphere, which comprise parts of the parietal lobule, precentral gyrus and inferior temporal gyrus. In addition, we report a partial congruency between clusters from sequencing studies and studies focusing on knowledge of tool use. These are associated with activation in the dorsal premotor area, posterior part of the intraparietal area, middle occipital gyrus and fusiform gyrus of the left hemisphere. In summary, ADL and single tool use are complex tasks with multiple aspects to be processed which recruit wide brain networks. Importantly it has to be stated that the neural bases of the three aspects discussed here cannot be clearly separated in actual tool use but need to be integrated to perform ADL. Evidence supporting the importance of the mentioned network is also provided by studies focusing on the neuronal basis of actual tool manipulation, which covered more general or other aspects of tool use (Hermsdörfer et al., 2007; Imazu et al., 2007; Gallivan et al., 2013). In addition, studies on pantomime of tool use also support the present findings (Moll et al., 2000; Inoue et al., 2001; Johnson-Frey et al., 2005; Króliczak and Frey, 2009; Vingerhoets et al., 2011).

LESION ANALYSIS IN PATIENT WITH BRAIN DAMAGE

Another method that sheds light on the neuroanatomical correlates of tool use is a lesion symptom analysis in CVA patients. In those studies, behavioral measures are correlated with lesion sites to create statistical brain maps showing the location of lesions closely linked to a behavioral deficit. Compared to the studies with healthy subjects, studies including lesion analysis focusing on executing or recognizing ADL are relatively rare (Pazzaglia et al., 2008; Goldenberg and Spatt, 2009; Randerath et al., 2010; Hermsdörfer et al., 2013; Kalénine et al., 2013). Therefore, a differentiation of action sequencing, conceptual understanding and spatiotemporal aspects of tool use, to the same extent as in healthy subjects or purely behavioral clinical studies, is limited. Hence, we aim to concentrate on studies including tasks testing performance of actual tool use and understanding or recognition of goal directed actions (Pazzaglia et al., 2008; Goldenberg and Spatt, 2009; Hermsdörfer et al., 2013; Kalénine et al., 2013). Additional information is given on the neuronal correlates of tool grasping next to tool usage (Randerath et al., 2010) and to increase the scope on the neural basis of sequencing ADL in patients, a study focussing on the sequencing of pantomime tool use (Weiss et al., 2008) will also be mentioned here.

In a study by Goldenberg and Spatt (2009), 38 patients with left sided brain lesions, were tested to assess possible deficits in functional knowledge of tools and objects, mechanical problem solving (which was tested with the use of novel tools), and additionally the selection and usage of common tools. Impairments in these tasks were related to two major lesions sites, one around the middle frontal gyrus reaching to the inferior frontal gyrus, which was related to deficits in all three tasks, and a second lesion site in the parietal cortex, reaching from the supramarginal gyrus through the inferior parietal lobule to the superior parietal cortex. The second lesion site mainly impaired the selection and use of common and novel tools. After looking at a subset of patients with deficits in the functional knowledge of tools (but not in mechanical problem solving) Goldenberg and Spatt (2009) found an association of this selective impairment to lesions in the middle temporal gyrus.

The relation of performance in tool use and lesions of patients with left sided brain damage was also analyzed by Hermsdörfer et al. (2013). Next to pantomime and imitation tasks, the correct performance of real tool use was measured and put in relation to the patients' lesions. In this study, low performance was also associated with parts of the inferior frontal gyrus including pars opercularis, triangularis, and insula.

As well as these two studies, which analyzed actual tool use, there are other studies focussing more on the understanding or recognition of actions. Kalénine et al. (2013) distinguish two parts of goal directed actions: action means and action outcome. The first component – dealing with "what" has to be done to achieve a goal (spatiotemporal features of the tool use) and the latter one – representing the actual outcome of the action (conceptual knowledge). Patients with left sided brain lesions, were asked to evaluate if two actions they saw in a video, were the same or different. These videos differed either in their action means or outcome. The performance of this detection task was combined with information from the patients' lesions, demonstrating a specific relation between lesions in the inferior parietal lobe with action means but not outcome. This underlines previously mentioned findings, stating the relevance of the inferior parietal lobe in processing the knowledge of what has to be done with a certain object or tool to achieve a goal.

The recognition of action related sounds and the execution of these actions was analyzed in a study from Pazzaglia et al. (2008) linking to the conceptual knowledge of tool use. Sounds of buccofacial-related or limb-related actions known from daily life had to be recognized by the patients and also executed. The lesion analysis revealed that impairment of action recognition and execution of buccofacial-related sound was mainly correlated with lesions in the inferior frontal gyrus and insula. Impaired limb-related action recognition and execution on the other side was associated with lesions in the inferior parietal lobe, supramarginal gyrus, angular gyrus, and also the inferior frontal gyrus. A stronger involvement of tool related parietal regions in limb-related action recognition, compared to buccofacial-related actions can be due to the fact that limb-related action sounds and executed actions included more tool actions, than the other condition.

Another lesion analysis including the analysis of actual tool use in patients with left sided brain damage was performed by Randerath et al. (2010). Patients had to grasp a tool and demonstrate its use for various tools with handles oriented toward or away from their body. In this study, the type of grasp (functional or non-functional) and the correct demonstration of tool use were evaluated and correlated with patients' lesions. The main findings related an impaired grip of tools to the lesions in the parieto-occipital junction, the angular gyrus, and especially in the inferior frontal gyrus, in particular the pars orbitalis, opercularis and triangularis. An incorrect demonstration of tool use on the other side was most closely linked to lesions in the supramarginal gyrus of the inferior parietal cortex and the gyrus postcentralis. An overlap between impaired grip and incorrect demonstration of tool use was found mainly in the inferior parietal cortex. As discussed by the authors, these findings are in line with the assumptions that the function specific manipulation of tools is mainly processed in the ventro-dorsal part of the dorsal stream (Rizzolatti and Matelli, 2003; for review see Binkofski and Buxbaum, 2012). According to this theory, reaching and grasping movements are related to dorso-dorsal regions like the superior parietal lobe, caudal parts of the intraparietal sulcus, parietal-occipital sulcus and the adjacent parietal-occipital junction (Karnath and Perenin, 2005; Prado et al., 2005). The findings of Randerath et al. (2010) underline the relevance of the parietal-occipital junction for correct grasping, especially for using tools.

To our knowledge, so far, only one study has performed a lesion analysis including sequencing of actions of daily living. In a study of Weiss et al. (2008) patients had to detect sequential and spatial errors in object related actions with or without the object. The main focus of the lesion analysis in this study was sequential error detection in actions without an object (pantomime of action). This analysis revealed that patients with severe problems in recognizing the correct timing sequence of an action had a common lesion site in the left angular gyrus of the parietal lobe.

In summary, the impairment in the recognition or performance of ADL including tool use was reported by many studies to be related to frontal lesions, especially the inferior frontal gyrus, inferior parietal lesions including supramarginal and angular gyrus and the neighboring parieto-occipital junction and lesions in the middle temporal gyrus. An overview of the affected regions and the associated tasks which were impaired, after lesions in these areas, is shown in **Figure 2**. Further evidence of the relevance of these brain regions in apraxia can be derived from lesion analyses focusing on pantomime of tool use. Again the ability to recognize pantomime of daily actions (Kalénine et al., 2010) or the execution of it (Buxbaum and Saffran, 2002; Buxbaum et al., 2005; Goldenberg et al., 2007; Hermsdörfer et al., 2013; Manuel et al., 2013) is strongly related to the already described lesion sites.

Considering the functional imaging studies on tool use and actions of daily living of healthy adults, we see a substantial overlap with the results of the lesion studies. For action sequencing, both imaging studies and lesion analysis show that the left angular gyrus plays a critical role. The conceptual understanding of tool use in ADL, on the other hand, comprises a larger network with core centers in the inferior frontal gyrus, the inferior parietal lobe and middle temporal gyrus. The neuronal processes of the spatiotemporal organization of actions in both healthy adults and also in patients were related to the posterior part of the parietal lobe including the angular gyrus, the parieto-occipital junction and the inferior frontal gyrus.

COMORBIDITY SYMPTOMS

As mentioned before, AADS syndrome might be enhanced by other comorbidity syndromes following a stroke (Goldenberg, 2013). The research that attempts to link different types of errors to other deficits that are co-morbid to apraxia in the CVA patients is partially unfruitful. One of the problems is that it is difficult to untwine which of the symptoms contribute the most to the difficulty with task execution. Around 30% of ischemic stroke survivors suffer from cognitive impairments apart from the motor disability, affecting speech ability, vision, memory and attention (Katz et al., 1999). For example, Walker et al. (2012) has demonstrated that dressing problems in the right brain damaged patients are mostly attributed to visuospatial deficits. In a similar vein, other studies have reported that visuospatial neglect (impairment of spatial attention) is a stable predictor for the functional outcome of the rehabilitation in the post hospitalization period (Denes et al., 1982; Edmans and Lincoln, 1991; Katz et al., 1999; Jehkonen et al., 2000). Other symptoms, such as hemiparesis, amnesia, visual construction problems and language deficits were reported to lack predictive power (Jehkonen et al., 2000). Importantly, this was contested by research conducted by Wade and Hewer (1987) pinpointing hemianopia (loss of side of visual field) as a second factor for functional recovery in post-acute phase of stroke. More recent work by Paolucci et al. (1998) has stated that absence of neglect is

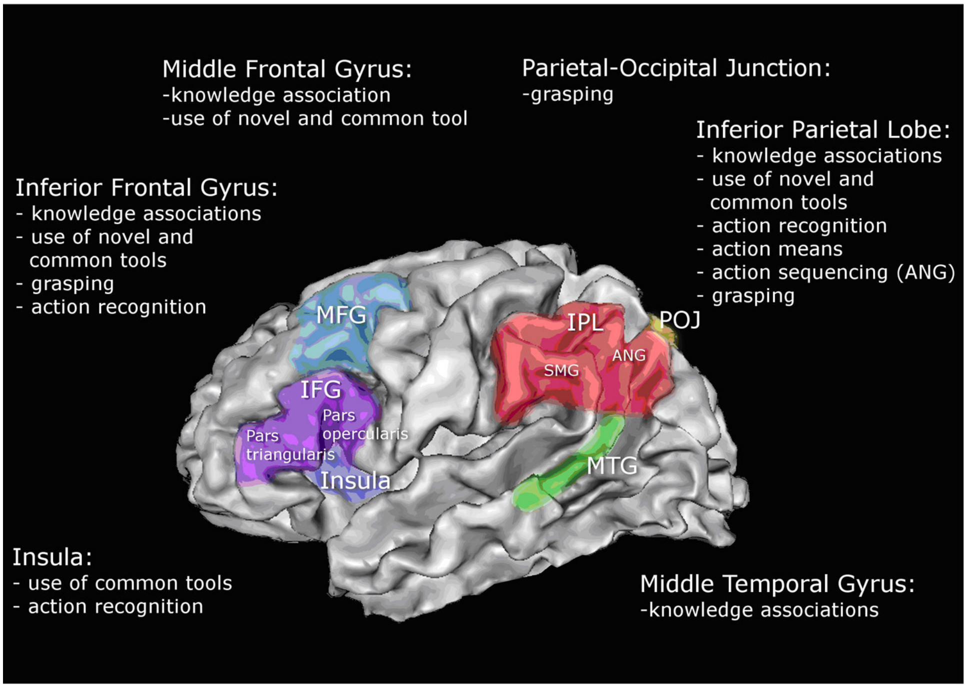

FIGURE 2 | Schematic illustration of left hemisphere associations with performance in tool use and ADL based on the reviewed studies; middle frontal gyrus (MFG); inferior frontal gyrus (IFG); inferior parietal lobe (IPL); supramarginal gyrus (SMG); angular gyrus (ANG); parietal-occipital junction (POJ); middle temporal gyrus (MTG).

the most important prerequisite for the promising prognosis for ADL independence. In addition, Pedersen et al. (1997) identified within the group of neglect patients that anosognosia (compromised self-awareness of own mental and physical state) is in fact a more powerful predictor of recovery in those patients. Therefore, many of the therapeutic approaches are targeted at broadening the visual field in patients suffering from hemianopia or hemineglect, through multisensory stimulations (Làdavas, 2008) or spatiomotor cueing (Kalra et al., 1997). The underlying assumption is that an effective rehabilitation plan needs to incorporate multicomponent factors and, in order to regain independence during ADL, a multifaceted approach is recommended – targeted at different neuropsychological symptoms (Katz et al., 1999). However, until now, there is no conclusive scientific evidence linking the severity of AADS with other neuropsychological symptoms, in particular, neglect. It is however clear that each of these symptoms has its own neural representation and a lesion will affect an aspect of ADL. These considerations reflect the difficulty to define a circumscribed neural network related to ADL. Rather, the network will be widespread with soft boundaries between areas directly and indirectly involved in action planning and tool use.

CONSEQUENCES OF APRAXIA AND AADS ON ADL, RECOVERY RATE, REHABILITATION

Although the incidence of apraxia is relatively high, the common view was that apraxia recovers spontaneously (Basso et al., 1987). However, this outlook is contested by the previous work of Hanna-Pladdy et al. (2003) and Smania et al. (2006) reporting that CVA patients struggle with ADL, due to residual traits of apraxia. Therefore, rehabilitation of apraxia maintains a significant challenge for the clinicians and occupational therapy workers. The research in this matter is inconsistent and limited in comparison to the number of studies investigating behavioral and neural correlates of apraxia (Goldenberg, 2013). According to Buxbaum et al. (2008) the common treatment approach is focused on teaching compensatory techniques for ADL tasks, which allow fostering independence despite the presence of apraxia. This strategy training comprises of the errorless training and high number of repetitions for particular task or verbalisation techniques (Goldenberg, 2013). In errorless approach the therapist guides the patient through the correct sequence of ADL and prevents the occurrence of action errors. In a similar vein, Buxbaum et al. (2008) reported that committing errors during training is disruptive for the outcome of retraining, thus compensatory strategies should be based on errorless approach. Goldenberg et al. (2001) states that intensive training improves specific task performance but cannot be generalized to other activities. In other words, training has to be task specific and does not transfer to other non-trained tasks (Goldenberg and Hagmann, 1998). Interestingly, in this report the majority of patients showed a deterioration of independence during ADL when therapy was withheld (2–5 weeks training period, daily 20–40 min). Exploration training, pointing out critical features of objects, without guidance how to use them did not bring improvement in patients (Goldenberg et al., 2001). Donkervoort et al. (2001) argues that strategy training may bring a short term benefit for patients and improve the global ADL functioning, but is the most effective in conjunction with standard occupation therapy. In their study intervention was based on verbalisation techniques comprised of providing narrative to guide through the task performance. Furthermore, another approach with evidenced efficacy is based on gesture training, which is more related to pantomime function (Buxbaum et al., 2008). This training is dedicated to practicing gestures associated with tool use. Smania et al. (2000) reported significant reduction in praxis errors and gesture comprehension after 35 training sessions (50 min each). In a subsequent study Smania et al. (2006) showed retention of gains 2 months post treatment after 30 training sessions of the same length as in previous report. In both studies, limited generalization to other tasks was found, but no impact on the overall ADL independence was noted. In addition, the home environment for training was pointed out to be important factor of recovery in 8 week intervention study (Geusgens et al., 2007). Tasks should be important for daily routine and meaningful for the patient. As summarized by Goldenberg (2013) AADS is not a homogenous disorder thus therapy approaches are usually adjusted to the core manifestations. Another aspect is that even if efficacy of training is maintained, it addresses primarily the ability to use compensatory strategies promoting independence during ADL, but does not affect the “concepts of use” (Goldenberg, 2013). Furthermore, the generalisability of training one task to global impact on ADL independence is often not assessed or not found, along with limited evidence for follow-up effectiveness (Maher et al., 1991; Pilgrim and Humphreys, 1994; Ochipa et al., 1995; Goldenberg et al., 2001). Consequently there is lack of clear guidelines what period of time is the optimal for treatment of AADS, which intensity of training is recommended and how to prolong the effects of therapy. Study by Goldenberg and Hagmann (1998) suggests that effects of the intervention can be only sustained if patient continues at home training of ADL independence. Training over the period of a few weeks is feasible if outpatient clinics or day clinics are in place. This, however, is increasingly challenged in the current economic climate, due to restricted funding for the post hospitalization phase. Therefore technology driven solutions might be soon developed to provide continuity for ADL training. In addition, if restoration of the function is impossible, rapidly developing technologies might soon provide a real time “crutch” for independence for stroke survivors. Use of the assistive devices in the home environment could provide additional contextual information for the patient in the ecologically valid setting. Contextual cueing was demonstrated by Maher et al. (1991) to improve performance of a chronic patient with ideokinetic apraxia (case study), within 2 weeks of therapy, based on the shaping (slow withdrawal of cues) paradigm. A similar idea was posited by Buxbaum et al. (2008) discussing the possibility of using robot-assisted devices.

Current projects, which aim to provide autonomous systems of guidance for patients struggling with ADL, are primarily tailored for subjects with dementia and use the concepts of domotics (intelligent home environment). One of the projects currently under development is the COACH system, which is designed to provide assistance in hand washing action to residents of nursing home for people with dementia (Mihailidis et al., 2008). Based on computer vision the system is capable of recognizing problems with task performance. The interface provides prompts based on verbal and visual information, with the prompts adjusted to the needs of patients (for example video or auditory cues). Another project, based on similar type of modeling and solutions is TEBRA, dedicated to aid tooth brushing performance in people with dementia in the home setting (Peters et al., 2013). Finally CogWatch (www.cogwatch.eu) is a system that is currently under development, which is tailored to the needs of AADS patients. The aim is to create fully automatised computer–human interface that provides cues or prompts errors during the performance of ADL (i.e., tea making and tooth brushing). Creating an autonomous system that could aid rehabilitation of ADL in AADS group is a technological and theoretical challenge, which surely will be pursued in the further research developments and projects.

CONCLUSION

The review summarized the most significant research conducted on the impact of AADS on the ADL in stroke survivors. Behavioral, neuroimaging and lesion studies were presented to give an overview of the current state-of-art. Taken together, CVA resulting in lesions in the left or/and right hemisphere has profound consequences on the daily independence of patients during everyday tasks such as food and drink preparation, grooming, personal hygiene, and use of everyday objects. A new approach was adopted to provide a comprehensive description of the unique features of apraxic and action disorganization disorder. The difficulties with execution of ADL were categorized arbitrarily into three components: problems with sequencing of the multi-step actions, conceptual knowledge about tool use and spatiotemporal aspects of the movement. This classification is novel in comparison to the original descriptions of AADS. However, the aim of this approach was to provide a comprehensive insight into the global picture of difficulties CVA patients might experience. Although these themes were presented separately, the evidence suggests those deficits are often intertwined on the behavioral level and also share the neural substrates. In the neural correlates section of this review, the critical role of the left angular gyrus was pinpointed in the sequencing of the multi-step actions. The neural underpinnings of conceptual knowledge were located in the inferior frontal gyrus, the inferior parietal lobe, and middle temporal gyrus. The spatiotemporal features of the execution of the ADL have been linked to the integrity of posterior part of the parietal lobe including the angular gyrus, the parieto-occipital junction and the inferior frontal gyrus. In addition, other areas that were also identified as linked to the ADL performance were discussed, with a conclusion that a wide neural network is involved in cognitive and motor aspects of action planning and execution. In the final section of this review, a strategy training approach was identified as the most efficient and common therapeutic strategy currently used in the rehabilitation of AADS.

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5 General Discussion – The Characteristics of the Tool Use Network

The Tool Use Network is left-lateralized, covers the ventral stream, parietal and frontal areas, shows a dorsal-to-ventral organization and is partly influenced by age.

The aim of this general discussion is to connect the different studies of this thesis and put them into context with theories and findings in the current literature. This discussion and comparisons are focused on conclusions that can be drawn considering the results and findings from the experimental and theoretical works included in this thesis. After a short summary of all three studies, common conclusions and main findings are discussed and compared to the current body of literature and theories. These include four major topics: (1) The lateralization of the tool use network; (2) brain areas included in this network and their associated function; (3) the organization of the dorsal and ventral processing stream and their role in tool use; (4) age-related changes of the tool use network with links to findings of patients with apraxia. An additional section emphasizes methodological advances and limitations of the experimental studies. The final section summarizes main messages and conclusions that can be drawn from this thesis and work of research.

Summary

Chapter two of this thesis includes the original research article "The neural correlates of planning and executing actual tool use" (Brandi, Wohlschläger, Sorg, & Hermsdörfer, 2014) and covers the fMRI study on the neural basis of real tool manipulations in young healthy adults. One major methodological goal of this study was to measure the planning and execution of real actions and object manipulations with fMRI. A method and apparatus, which allows analyzing the use of multiple tools known from daily life and a variety of unknown neutral objects in the MRI environment, was aimed to be established. Additionally, this study addressed questions about the brain's function and the neural underpinnings of tool use: The main focus laid on the question how the factor object (known tool or neutral objects), task (functional use or transport) or hand (dominant or non-dominant hand) influences the neural pattern and structure of the brain network which is responsible for processing tool use actions. Furthermore, one important element was to look on the phase of planning an action as well as the real execution. The results showed that the manipulation of tools recruits a left-lateralized network with ventral stream activations (pMTG and LOC), parietal lobe activations (posterior parietal cortex, SMG and AIP) and frontal activations. Both action planning and execution recruited similar brain areas, but action execution included stronger frontal brain involvement (PMv, PMd, MFG, insular cortex). The comparison between task types, showing those areas responsive to increased online control of actions and higher demands on movement monitoring, revealed that regions of the dorso-dorsal stream as well as LOC are involved. Areas showing the highest selectivity for known object manipulations like tool use are associated with the ventro-dorsal stream described previously. A ventral stream area (MTG) was co-activated with the dorsal stream in this analysis, too. The analysis of the hand used revealed that actions done with the non-dominant hand increase the recruitment of the whole left-lateralized network necessary for tool use actions. Five main conclusions can be drawn from this study: (1) The "Tool-Carousel" is a suitable apparatus and method to measure real actions with fMRI; (2) the tool use and action network is strongly left-lateralized; (3) action planning and execution of tool manipulations recruit a similar network including temporal, occipital, parietal and frontal brain areas; (4) the division of the dorsal stream (Binkofski & Buxbaum, 2013) can be seen in real actions with neutral objects and tools; (5) ventral stream brain areas are co-activated with the dorsal stream, suggesting connections and interactions of both streams while performing real actions.

The second research manuscript "Age-related changes in the neural correlates of complex object manipulations" included in this thesis (Brandi, Hermsdörfer, Sorg, & Wohlschläger, unpublished) also covers the analysis of real actions in the MRI scanner, but added the examination of elderly adults. The main research aim of this study was to compare the neural structure and pattern of the tool use and action network between young and healthy adults and evaluate age-related neural changes. Furthermore, it was tested if two existing theories on possible mechanisms in the aging brain could be applied to the neural processes of object manipulation in the elderly brain. The analysis revealed that both young and elderly show a similar left-lateralized brain pattern during actions with tools compared to neutral objects and during using compared to transporting actions. Elderly show an increased neural recruitment during action planning but decreased activations during execution compared to healthy young individuals. Elderly show a similar selectivity for objects and tasks in the brain areas of the tool use network like young adults, but increased brain activation in the frontal lobe and posterior parietal lobe in relation to their behavioral performance. Overall, the results of the study lead to four main conclusions: (1) The tool use and action network described before is mainly stable across age; (2) the activation strength in elderly compared to young individuals shifts to the planning phase of an action; (3) compensatory mechanisms could be found, while dedifferentiation effects could not be clearly detected; (4) due to the age-related differences found in healthy elderly individuals, comparisons of fMRI studies of healthy participants with apractic patients should include an age-matched sample to get a more accurate understanding of tool use and the neuroanatomical correlates of apraxia.

The third article included is called “The tool in the brain: apraxia in ADL. Behavioral and neurological correlates of apraxia in daily living.” (Bieńkiewicz et al., 2014) and contains a literature review on behavioral studies on apraxia and the action disorganization syndrome. Additionally, it covers a review on the neural basis of tool use, focusing on fMRI studies from healthy adults and lesion analyses from stroke patients with apraxia. The main goal of this review was to provide an overview of the current literature on behavioral and neuroanatomical findings about apraxia, especially focusing on three essential error types observed in patients: Sequencing errors in multi-step actions, conceptual errors and spatio-temporal errors in tool use. Based on this categorization of error types, brain imaging studies of healthy subjects dealing with the sequencing of multi-step actions, the conceptual understanding and spatio-temporal processing of tool use were summarized and visualized. Additionally, lesion analyses with patients suffering from apraxia and impairments in tool use were discussed and also compared to the findings of healthy adults. Because the contribution to this review by the author of this thesis comprised the summary and comparisons of the neural correlates of sequencing, conceptual understanding and spatio-temporal processing of tool use in healthy adults and the lesion analyses, only this part can be regarded part of this thesis. Therefore, the focus of the summary and discussion will mainly lay on these aspects. Considering the review on findings of healthy participants and patients three main conclusions can be made: (1) Three different networks can be defined which code the sequencing of actions, the conceptual understanding and the spatio-temporal processing of tool use after summarizing neuroimaging studies of healthy adults analyzing those aspects of tool use; (2) patients with apraxia show lesion sites in relation to tool use impairments in several locations of the brain including the parietal cortex, the MTG, the inferior and middle frontal gyrus and the insular cortex; (3) taking both findings together it can be stated that the spatio-temporal processing of tool use is associated with the posterior part of the parietal lobe, while the conceptual understanding of tool use is related to a more widespread network with temporal, parietal and frontal contributions. Sequencing errors in patients and activations in healthy adults are mostly related to the angular gyrus of the parietal cortex.

Common conclusions from all studies and associations to current literature

Taking together all findings and conclusions resulting from the two experimental studies (Brandi et al., 2014; unpublished) and the literature review (Bieńkiewicz et al., 2014), several general statements can be made about the tool use network: (1) The tool use network is clearly left-lateralized in real actions independent of the hand used to do the action and independent of age. This finding is further strengthened by the lesion studies including patients with left-sided brain damage and symptoms of apraxia; (2) the brain regions found to be relevant for planning and executing real tool use and actual object manipulations overlap and are in line with the neural network found in previous research on tasks related to tool use and with observations of brain damaged patients and tool use impairments; (3) the general pattern of brain activations during actual tool use seen in the two experimental studies but also in the studies presented in the review, show a gradient from overall spatio-temporal control of hand and arm coordination processed in the dorsal brain to processes with a stronger semantical influence in the ventral brain; (4) age-related mechanisms and changes in the tool use network have to be considered for comparisons with cases of apraxia to get a more accurate view on the neural underpinnings of such tool use and action impairments. The next paragraphs discuss all four points in more detail and relate the findings of the experimental work and the review to each other and to further current literature.

Lateralization

As depicted in the experimental studies and the review, the network related to real actions with known tools and objects is mainly lateralized to the left hemisphere. This result is strongest and most consistent for tool actions compared to actions with unknown objects and also stable in age. Additionally, it was shown in young adults that this lateralization is also independent of the hand used (Brandi et al., 2014, unpublished). This can be confirmed by studies on the neural correlates of pantomime of tool use performed with both the dominant and the non-dominant hand (Johnson-Frey et al., 2005). In the literature review the left-sided lateralization was strongest in the analysis of the conceptual understanding of tool actions in healthy adults (Bieńkiewicz et al., 2014). Clearly, the importance of the left brain in tool use actions, but also in pantomime and gesture production is further strengthened by clinical observations apractic patients who mainly suffer from symptoms after left-sided brain damage (Goldenberg, 2014).

Lateralization is not a phenomenon that is only found in tool use actions. The neural processing of language, a characteristic human ability, is lateralized to the left side of the brain and probably the most common example of hemispheric lateralization. Since the research performed by Paul Broca, it is known that those brain areas relevant for speech production are located on the left side of the brain (Broca, 1861). The fact that both the development of complex language and tool use are defining abilities of the human species and both lateralized to the left hemisphere, is in favor of the hypothesis that the evolutionary development of both abilities are connected (Corballis, 2012; Steele, Ferrari, & Fogassi, 2012). Corballis assumes that the connection between actions with hands and language is caused by the fact that language originated from hand gestures. It is believed that language evolved from the primate mirror system which is originally relevant for the recognition and performance of grasping movements (Corballis, 2012). Later in development communication was not based on gestures anymore but included vocals which led to the advantage of freeing the hands for actions, tool use and for teaching and demonstration (Corballis, 2003). Considering the parallel development of tool use and language it is plausible that the general brain structures of both processes also evolved similarly and show the same lateralization, but it does not explain why the process is lateralized. Still the answer to the question why the brain develops asymmetries for certain functions is not fully clear. One prominent theory is that the lateralization of one function to one side of the brain increases the neural capacity. This means, if the neural process of one specific task or purpose is related to only one hemisphere, the other hemisphere can specialize on further other functions (Levy, 1977). This would reduce unnecessary duplication of functional specified brain location in both hemispheres and increase the brains efficiency and capacity to allow simultaneous processing (Halpern, Güntürkün, Hopkins, & Rogers, 2005; Vallortigara & Rogers, 2005).

Alterations of brain lateralization are often found in the aging brain. In the study on elderly individuals in chapter three the age-related changes in the lateralization are dependent on which brain network is looked at. As mentioned before, the pattern of brain areas active for tool actions compared to actions with unknown objects as well as those brain areas active for using objects compared to transporting them are clearly left-lateralized in age. On the other hand, a comparison of the brain activations during action planning of any actions in elderly to young adults results in a clear bilateral pattern including the same areas known to be relevant for tool use and other object manipulations. This result is in line with a wide range of literature showing an age-related over-recruitment of brain activation on both hemispheres (Cabeza, 2002; Grady, 2012). This phenomenon of decreased lateralization is either interpreted as a loss in efficiency or as a mechanism recruiting additional resources to compensate for age related structural changes in the aging brain (Grady, 2012). This topic will be discussed further in the section "Elderly and Apraxia".

Another interesting factor related to the brains' lateralization in tool use actions is handedness. The development of having a dominant hand lead to an increase of motor skills and movement precision in one hand, which therefore is specialized for complex manual actions. The development of right hand dominance in most humans to perform actions, which is based on the control of the contra lateral brain, is assumed to be connected to the development of the left-sided lateralization in language and tool use (Frey, 2008; Steele et al., 2012). As it was shown in the study with healthy young adults and elderly in chapter two and three, the left-sided lateralization is also present during non-dominant hand use in right handers. This emphasizes the essential role of the left hemisphere in tool use independent on the hand used in right handed participants (Brandi et al., 2014, unpublished). Studies including left-handers are rare and the question if hand dominance has an impact on lateralization is not clear. Planning grasping actions with the hand and a tool (Martin et al., 2011) as well as the pantomime of tool use (Vingerhoets et al.,

2012) is less lateralized to the left side with more bilateral activations in left handers independent of the hand used. Bilateral activations were seen in the IPL and SPL for tool use pantomime and aIPS and PMv during grasp planning. In general it can be said that independent of handedness both tasks (but especially pantomime) show a left-sided lateralization but reduced in left-handers (Martin et al., 2011; Vingerhoets et al., 2012).

In respect to apraxia, the side of the brain lesion connected to impairments of imitation, single tool use and pantomime of tool use is the left and this finding is also referred to as one of the "core manifestations" of apraxia (Goldenberg, 2014). Impairments in the production of communicative gestures and pantomime with a strong left-sided lateralization of brain lesions can be assumed to be connected to the close relation to language and brain damage in the language dominant hemisphere (Frey, 2008). But not only lesion of the left brain can cause symptoms related to apraxia (Bieńkiewicz et al., 2014), also right brain damaged patients show impairments in actions of daily living related to tool use (Hartmann, Goldenberg, Daumüller, & Hermsdörfer, 2005). These impairments are mainly related to actions with multiple steps, the use of novel tools and the imitation of gestures (Goldenberg & Hagmann, 1998; Goldenberg, 1996; Hartmann et al., 2005). In more detail this means, right brain damaged patients seem to be most impaired in sequencing action steps (Hartmann et al., 2005) and also in the visuospatial evaluation of demonstrated gestures (Goldenberg, 1996). This leads to the conclusion that sequencing and also spatial processing of actions are not only related to the left but also to the right hemisphere. This assumption is in line with the literature review of healthy adults in chapter four which shows bilateral activations in fMRI studies on sequencing and spatio-temporal features of actions.

Considering these findings and the patient studies mentioned above, it seems that action processes like sequencing action steps and the spatio-temporal control of objects have additional right brain involvement compared to language-related tool gestures and tool use actions, which are strongly left-lateralized.

The Tool Use Network

As described in chapter one the act of using a tool can be subdivided in different elements which are processed by a distinct network of brain areas. These elements include the process of object recognition, recalling the knowledge of object function and how to manipulate it, reaching, grasping and the execution and online control of the action. The neural basis of these elements has previously been analyzed by different approaches, for example viewing, imagining or pantomime of tool use actions and found a variety of different brain circuits which process information relevant for tool related tasks. The two experimental studies presented in chapter two and three, support and extend these findings to characterize the network during actual tool use for young and elderly adults. Importantly, here the network was not only described at the time point of execution, but also during action planning. A similar network was found for both action phases underlining the importance of the recruited brain areas for the whole time course of an action and tool use (Brandi et al., 2014, unpublished).

Object recognition and processing concerning object properties were found to be located in temporal and occipital areas as well as the fusiform gyrus in the ventral stream (Grill-Spector & Malach, 2004; Milner & Goodale, 2008). Similar results are also shown in the experimental study with healthy participants for planning and executing real tool related actions (Brandi et al., 2014, unpublished). LOC, MTG and a cluster in the fusiform gyrus are recruited during planning tool use actions in both elderly and young adults and underline previous articles which show the selectivity for object properties and tools in these areas (Chao et al., 1999; Grill-spector et al., 2001). Studies looking at preparatory brain activations show that occipito-temporal brain areas are relevant for processing object properties in order to conduct real goal-directed object manipulations also and extend the role of the ventral stream from processing perceptual information to a high influence in planning actions with objects (Gallivan et al., 2013; Gallivan, Johnsrude, & Randall Flanagan, 2015).

The neural basis of the conceptual understanding of tool use summarized in the literature review included studies testing context dependent tool use, tool familiarity, conceptual understanding and correctness of tool use in actions of daily living (Bieńkiewicz et al., 2014). A high involvement of the anterior parietal cortex, premotor areas and the MTG of the left next to fewer clusters in the right hemisphere can be seen. In the fMRI study with healthy young adults similar results are shown for those regions mostly selective for goal directed actions with tools. These include the MTG, anterior SMG of the inferior parietal lobe and the PMv (Brandi et al., 2014). In comparison to the literature this circuits overlap with those brain areas coding the knowledge about the objects function (Chen, Garcea, & Mahon, 2015) as well as those processing the knowledge of how to use a tool (Buxbaum & Saffran, 2002). Especially the latter aspect of tool use is a topic of discussion: The knowledge of how to use a tool, which was referred to as manipulation knowledge previously, is often described as an “gesture engrams” and it is assumed to be a form of semantic memory coded mainly in the parietal lobe and disrupted in patient with apraxia (Boronat et al., 2005; Buxbaum & Saffran, 2002; Pelgrims et al., 2011). It is questionable if manipulation knowledge is a coded memory in the brain and this assumption is challenged by another possible theory (Goldenberg, 2009; Osiurak, Jarry, & Le Gall, 2011; Sunderland, Wilkins, Dineen, & Dawson, 2013). It hypothesizes that those brain areas, which have been found to be closely connected to known object manipulations, like the inferior parietal lobe, do not represent an engram, but are rather essential for mechanical problem solving and integrating information about the functional relevant parts and properties of objects for goal directed manipulations (Goldenberg, 2014). The results mentioned previously and presented in chapter 2 are showing those brain areas most selective for tool use. This activation pattern could represent coded manipulation knowledge but also increased demands on mechanical problem solving. Due to the fact that the condition tool use in the fMRI study is the most complex action in terms of the included object properties and chain of mechanical problems, it can be argued that increased demands on mechanical problem solving causes the brain activation. Considering this discussion in the current literature it can be said that even though the exact function of the inferior parietal lobe in tool use is not fully clear, it is for certain that flawless performance of goal directed actions with tools depends on it.

The brain networks processing spatial coordination of arm, hand and fingers for reaching, grasping and monitoring object manipulations was of relevance in all three included articles. Both planning and executing actions with higher demands on reaching, grasping and monitoring recruited posterior parietal and dorsal premotor areas in both experimental studies. Additionally, the literature review underlines these findings in the summary of spatio-temporal processing of tool use in healthy subjects. Here, the superior and inferior parietal lobe, pIPS, POJ/SPOC, dorsal premotor cortex and the middle occipital gyrus in both hemispheres are related to correct grasping and spatial control of movements in tool use actions (Bieńkiewicz et al., 2014). In comparison to the lesion data of patients with apraxia erroneous tool grasping is also related to the POJ and inferior frontal gyrus (Bieńkiewicz et al., 2014; Randerath et al., 2010). Overall, these results are in line with the presented literature in chapter one and further characterize the functional relevance of the neural circuit including the posterior parietal lobe and premotor areas responsible for planning and executing the correct arm, hand and finger postures for interactions with objects as well as the control of use-related movements.

In summary, it can be concluded that actual tool use in young and elderly adults goes along with the recruitment of ventral stream areas for visual processes, inferior parietal and frontal activations related to tool use actions in particular and posterior parietal and PMd activations associated with the control of complex reaching and grasping movements. Figure 2 summarizes and visualizes the results and gives an updated model of the tool use and action network described in chapter one, which is relevant for the young and elderly brain, as well as both planning and executing actions.

Dorsal-to-ventral organization of the tool use and action network

The previous section discussed the experimental and reviewed results covering different brain areas relevant for specific functions related to tool use. When not focusing on individual locations and functions of brain areas only, but describing the organization of the action and tool use network as a whole, additional conclusions can be drawn. The results of the fMRI analysis show that the online control of complex actions independent of object type is processed in a dorso-dorsal processing stream, while ventro-dorsal areas process known tool use in real actions (Brandi et al., 2014). Importantly, ventral stream areas are co-activated with these pathways. The literature review shows a similar pattern, with strong dorsal involvement in spatio-temporal processes and increased ventral activation and lesion sites related to the conceptual understanding of tool use (Bieńkiewicz et al., 2014). Overall, these findings and the current literature show that the pattern of brain areas relevant for an action show a "dorsal-to-ventral" organization dependent on the amount of semantic processing involved in the action. This means in detail: An action which is only related to the spatial control of objects independent of identity is processed in a rather dorsal location of the brain, while increased semantical meaning in an action also increases the involvement of additional ventral brain areas recruited. This assumption extends the view of two separated streams, one for action processing, the other for perception and recognition (Goodale & Milner, 1992). It is rather a dorsal-to-ventral gradient which describes interconnected subnetworks relevant to perform different kinds of actions. This assumption is based on the hypothesis that the dorsal processing stream can be divided into two pathways as mentioned before. A dorso-dorsal route is relevant for the control of online actions and the monitoring of objects in space, while the ventro-dorsal route is connected to action semantics and known object manipulation connected to a certain meaning (Buxbaum & Kalénine, 2010; Buxbaum et al., 2006; Kalénine et al., 2010; Rizzolatti & Matelli, 2003). A lesion analysis with patients suffering from apraxia underlines this assumption and also emphasizes the role of the ventral stream in actions (Hoeren et al., 2014). The imitation of meaningless gestures is associated with lesions in dorsal brain, while the pantomime of tool use is related to lesions in the ventro-dorsal stream and also the ventral stream, in this study. Additional fMRI and DTI analysis on imitation and pantomime show similar findings concerning the dorsal-to-ventral organization in healthy individuals on a structural brain level and underline the interconnection of IFG, MTG and IPL by ventral fibers relevant for semantical actions like pantomime (Vry et al., 2014). Further insight can be given by another type of connectivity analysis focusing on functional co-activations of brain regions during rest. The analysis is based on the assumption that brain areas which share a common function show a coherent activation pattern during rest and are therefore connected (van den Heuvel & Hulshoff Pol, 2010). The functional connectivity pattern of the MTG with the rest of the brain shows that it is highly linked with the anterior inferior parietal lobe as shown in the DTI study mentioned above, but also with other brain areas like the middle-to-anterior IPS, postcentral gyrus, POS, precuneus, SPL, insular cortex, middle frontal gyrus, the inferior frontal gyrus and the dorsal and ventral premotor cortices (Hutchison, Culham, Everling, Flanagan, & Gallivan, 2014). In this study another ventral stream area was revealed to have connections to other dorsal stream areas. The left LOC shows a functional connectivity with the POS and the posterior IPS, two brain regions previously reported to be relevant for the control of objects in space. Considering the LOCs involvement in processing grasping relevant object related properties (Monaco et al., 2011), this functional connection seems plausible. The connection between ventral and dorsal stream areas was also tested with functional task-related activity including tools as visual stimuli

(Almeida, Fintzi, & Mahon, 2013). The authors argue that the access of tool manipulation knowledge, which is related to the inferior parietal cortex, strongly dependents on retrieving semantic or identity information of objects via the ventral stream. Dynamic causal modelling (DCM) provides another connectivity analysis which can be used to analyze connections in the action network (Friston, Harrison, & Penny, 2003). A DCM study on grip-selection of useable objects from daily life showed that the demands of grip-selection alters the dynamics of a network including AIP, pMTG and PMv as important nodes (Makuuchi, Someya, Ogawa, & Takayama, 2012). The connection from pMTG to AIP is altered with increased load on the selection of grip type as well as the converging interactions from pMTG and AIP to the PMv. The authors emphasize the interaction of ventral and dorsal stream for the process of grasping usable objects and the integrating role of the PMv for the selection of the correct hand shape for grasping.

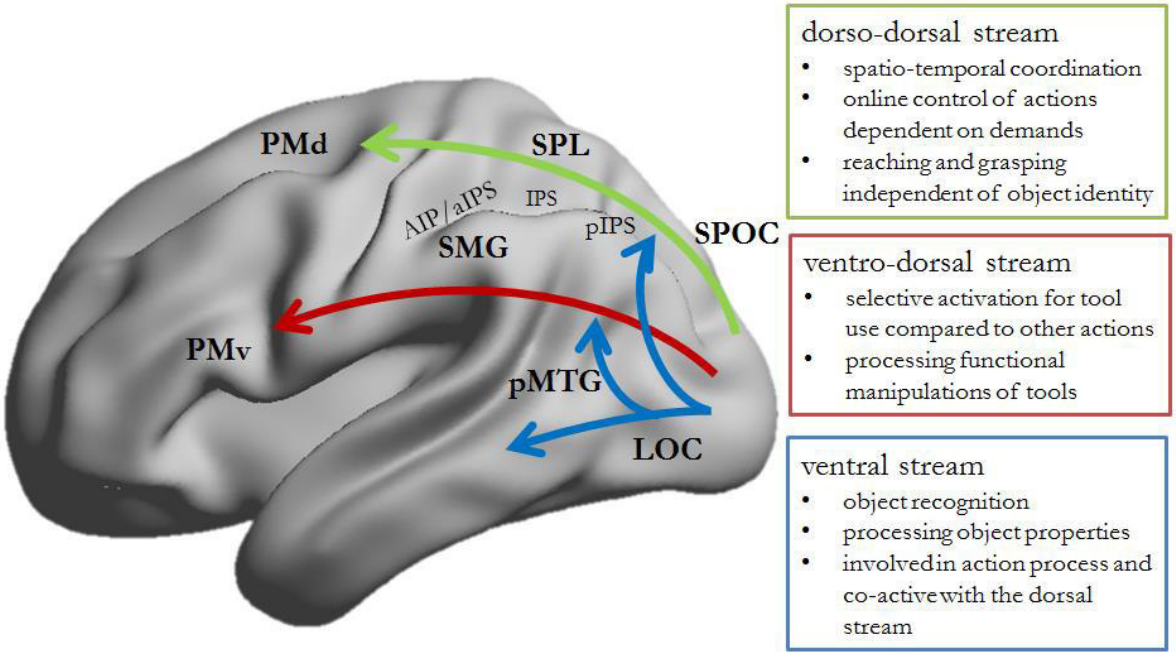

Figure 2: An updated model of the organization of the network relevant for tool use and actions. Shown are the dorso-dorsal stream in green, the ventro-dorsal stream in red and the ventral stream in blue on a rendered left hemisphere of the brain. This model is applicable for elderly individuals and the visualized brain network is relevant for both planning and executing actions.

To conclude, the reported results and current literature lead not only to the assumption that the pattern of processing streams is dependent on the semantic involvement of an action, but also that these processing streams described previously are not strictly separated during tool use, but are interconnected. Semantic information, which is associated with ventral brain areas, has to be coupled to those processing streams relevant for action. This means that ventral stream areas like the MTG and LOC are not only involved in perception but also in actions and are therefore co-activated with the dorsal stream during real actions or action-related processes with tools. This is shown to be the case in real actions in the experimental study with healthy young and elderly adults (Brandi et al., 2014, unpublished) as well as in the literature review (Bieńkiewicz et al., 2014). The hypothesis that information from the ventral stream has to be transferred to the dorsal stream is also included in the updated model of the tool use and action network in Figure 2. Further connectivity analyses could confirm whether the found co-activation goes along with an increased coupling between the proposed connections during actual action planning and execution.

Elderly and Apraxia

Healthy aging has an effect on the neural process of different cognitive and motor functions and therefore also on behavior. How the brain network necessary for conducting actions with tools is altered due to age-related brain atrophy had not been analyzed before until now. As it was presented in chapter one, several aspects of tool use like semantic processes, reaching, grasping, fine motor skills and precise movement control are influenced on a behavioral and neural level. The fMRI analysis on healthy elderly adults supports these findings and gives new insights into the alterations that affect the neural correlates of tool use and general object manipulations (Brandi et al., unpublished). The strongest change that could be observed was an increased activation during action planning in elderly adults compared to young adults, which covered a wide bilateral network including the anterior and posterior parietal lobe, ventral stream areas like MTG and LOC as well as premotor areas of the frontal cortex. Therefore, key areas in the neural tool use and action network seem to show an altered activation pattern in elderly adults during the preparation of actions in general. The relative difference of activation strength between the tested actions was not accompanied by age-related changes. Therefore, a dedifferentiation or decrease in selectivity within the tool use and action network could not be detected in the elderly brain. Interestingly, the effect of over-activation is restricted to the planning phase which leads to the conclusion that this phase of an action needs stronger resources in the elderly brain in order to perform a task. One explanation as described before is that the increased activity in elderly is necessary to ensure accurate or correct performance (Grady, 2012; Ward, 2006) and represents a compensatory mechanism. In general, compensatory mechanisms are usually assumed if the increased activity is associated with similar performance like in young adults or if the activity strength of elderly is correlated with better performance while there is no such correlation in young individuals (Grady, 2012; Heuninckx et al., 2008). The latter was the case in the fMRI study included in this thesis and mainly showed a relationship between good performance and increased activation strength in the frontal cortex (bilateral MFG reaching to IFG) and two left-sided posterior parietal regions (SPOC and pIPS). The existence of such a mechanism is questioned, especially due to inconsistencies in the results and the relations between behavioral scores and brain activity. Some researchers argue that increased recruitment with similar performance is rather a sign of inefficiency of activated resources than a compensatory mechanism (Grady, 2012; Spreng et al., 2010; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007). Other studies even found that over-recruitment in frontal areas is related to worse or slower performance in elderly compared to younger adults in different memory or visual tasks (de Chastelaine, Wang, Minton, Muftuler, & Rugg, 2011; Grady, 2012; Grady et al., 2010). It seems that there is no clear relation between brain activity and task performance in the elderly brain that can explain alterations in the aging brain across cognitive domains and tasks. One model, which tries to explain compensatory activation as they were found in the fMRI study with elderly adults in chapter two, is called CRUNCH ("compensation-related utilization of neural circuits hypothesis") (Reuter-Lorenz & Cappell, 2008). It also takes the level of cognitive load of a task into account and assumes that at lower load elderly need more neural resources for a task than young adults while at higher load such a compensatory mechanism is not efficient any more. This results in similar or even lower activation strength in elderly individuals. Such activation patterns have been found to be present in frontal and parietal areas during a working memory task (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Schneider-Garces et al., 2010) and this theory therefore provides a possible explanation for increased and decreased activations in elderly compared to young adults. Based on this theory, the decreased activation strength during the execution of an action in elderly compared to young adults, reported in chapter three, could be explained by an inefficient compensatory mechanism due to increased demands on action control. Another possible explanation could be that the elderly show differences in kinematic parameters of the hand movement. Decreased grip force, movement speed and dynamics could also lead to lower activations compared to young adults. A detailed kinematic analysis of hand actions in the current experimental design was not possible, but would enhance the understanding of age-related changes in the neural processing of action execution (Brandi et al. unpublished).

Even though the study presented in chapter three could not provide detailed information about movement kinematics, still behavioral changes in tool related actions were detected (Brandi et al., unpublished). While some of the errors made by the elderly are not directly related to object manipulations but rather to possible attention deficits resulting in incorrect actions in relation to the experimental cue, others are clearly associated with incorrect object grasping and movements for correct use. Additional to the data presented here, also other studies found impairments in elderly related to tool use actions. Pantomime of tool use, which is known to be impaired in apraxia, is also affected by aging. Elderly adults often show body-part-as-object errors during pantomime, which means shaping the own hand as the acting tool and not creating a hand posture to grasp it (Peigneux & van der Linden, 1999; Rodrigues Cavalcante & Caramelli, 2009; Ska & Nespoulous, 1987). Also the recognition of transitive (object related movements like tool use) and intransitive (movements not related to tools like waving) hand postures is shown to be reduced in elderly adults (Mozaz, Crucian, & Heilman, 2009). This does not mean that elderly individuals have a form of apraxia, but it shows that age-related changes can lead to impairments in an aspect of tool use similar to what is seen in the symptoms of patients with apraxia (Mizelle & Wheaton, 2010).

The observation of impairments in behavior in brain damaged patients and the association of those deficits to lesion locations help to understand the neural network responsible for that particular behavior. Considering that the age of patients with brain damage, for example after stroke, is similar to an elderly population, it has to be taken into account that the damaged brain network analyzed might also been affected by age-related changes. Therefore, when analyzing the neuroanatomical basics of apraxia and tool use, it has to be deliberated that the neural correlates of planning and executing tool use might be affected by age in these patients as well. The role of compensatory mechanisms, the bilateral increase of activation during action planning and additionally the shift to stronger activations in the planning compared to the execution phase of an action should be considered in the connection of lesion locations and the role in tool use of the affected brain area. In the literature review of lesion analyses in chapter four, several brain areas were associated with erroneous tool use actions like the middle temporal gyrus, middle and inferior frontal cortex, the inferior parietal lobe as well as a few posterior parietal areas (Bieńkiewicz et al., 2014). As reported, these areas are essential for gestures, tool use or tool related actions, but also include regions that have been shown to represent a compensatory mechanism ensuring accurate performance of object manipulations in this thesis (Brandi et al. unpublished). Additionally, the phenomenon of increased bilateral recruitment of brain areas for compensation during action planning might also attribute to the fact that errors in multi-step actions are also related to damages in the right brain. While these assumptions present some additional explanations to the neural basics leading to the symptoms of apraxia, further research is needed to prove that age-related neural changes play a role in the behavioral deficits of patients with the symptoms of apraxia.

Methodological advances and limitations

The methods developed and presented in this thesis provide the possibility to characterize the neural correlates of real hand-object interactions and therefore enable further insight into the brain processes of a variety of object manipulations and in specific tool use across age (Brandi et al., 2014, unpublished). This section aims to summarize the advantages of the materials and experimental design used in the included experimental studies, discuss possible limitations, improvements and perspectives.

The "Tool-Carousel" is a suited apparatus to present a variety of different stimuli which can be grasped and manipulated by participants during an fMRI measurement. Previous studies have used similar devices to include objects in the MRI environment (Culham et al., 2003; Gallivan et al., 2013; Valyear et al., 2012), but none of these enables the experimenter to present a variety of different real sized objects in a short period of time with accurate onsets in a controlled visual field. Furthermore, the inclusion of an unpredictable go-cue for action induces the participant to plan an action in every trial even though the real action is only cued in a subset of trails. Therefore, these methods allow analyzing the neural correlated of action planning without movement artefacts confounding the activations and confirm the findings that preparatory brain activations are similar to those necessary for the actual movement. One possible extension of this analysis would be to use these planning signals and detect if these preparatory activations can predict an upcoming action and in which areas this is the case. This can be achieved with multi-voxel pattern classification which is very sensitive to detect the selectivity of brain activations for different upcoming tasks and has been used before to analyze preparatory activations of real actions (Gallivan et al., 2013; Gallivan et al., 2015, 2011).

One limitation of the method presented here, which also has to be considered, is the use of a mirror system on the head coil to provide visual feedback for the participants. It can be argued that this fact adds an additional visuospatial transformation to the task, because the participants do not have a direct view on their hands as it is possible with a tilted head coil (Culham et al., 2003). Under the circumstances of the MRI scanner used, a tilted head coil or simply tilting the head in the existing coil, was not possible. The limitations emerging from this technical constraint can be minimized by the fact that such transformations are present in all experimental conditions and should be cancelled out in the comparison analysis.

As shown in the study with elderly participants, the "Tool-Carousel" also allows measuring different subject groups and not only healthy young adults. The development of the tool use network across the whole lifespan as well as the analysis of tool use difficulties in different mild impaired patient groups would be possible. Functional and structural age-related neural alterations, which lead to the previous described changes in grasping, transitive gestures and tool use, could be defined and compared to patients with the same impairment in equal tasks to investigate different brain modifications which lead to equivalent behavioral deficits. The inclusion of behavioral scores, which were gathered with a video camera and a motion detection analysis, extended the possibility to analyze the participants' actions and set their performance in relation to the brain activations. This is a valuable approach which was of special interest in case of the elderly study and the analysis of compensatory mechanisms (Brandi et al. unpublished). Such analysis could be further improved with more accurate and detailed video recordings and motion capturing cameras tracking more movement parameters of hand actions. This could enhance future analyses of real hand actions and, for example, make the detection and characterization of errors and movement impairments in elderly individuals or patient groups more precise.

Taken together, the “Tool-Carousel” and the experimental design represent an adequate approach to study the neural correlates of tool use in young and elderly adults and provide a good method for future research on the neural basics of different actions across age.

Conclusion

The use of objects as tools is an ability that humans developed millions of years ago and that has developed to become an essential element of our lives. The brain network responsible for these actions has been of interest to several researchers but is still not fully understood. The characterization of this network, responsible for using a spoon, a pen or a hammer, during fMRI measurements is a methodological challenge which was met in the experimental studies included in this thesis and extended by a literature review. The main goals of this thesis were to gain a better understanding of the composition of the tool use network, its hemispheric organization, the location of different functional pathways, and its age-related alterations as well as a comparison of fMRI results of healthy individuals and lesion analyses of patients with apraxia and impairments of tool use actions. The measurement of planning and executing real tool use with fMRI, the examination of the same in an elderly group and the review of clinical observations of tool use impairments after brain damage provide new insights for the understanding of the neural process underlying human tool use: The tool use network is left-lateralized, independent of the dominant or non-dominant hand used, and the network’s lateralization is stable in age. An overall bilateral over-recruitment of brain areas in the elderly is present in action planning and should be considered in the discussion of possible reasons for impairments in activities of daily living and right brain damaged patients. Brain areas found for planning and executing real actions with tools and neutral objects overlap with previous fMRI and lesion studies of patients suffering from apraxia and are also recruited in elderly. These include areas of the ventral stream for semantic processes, posterior parietal regions for monitoring the spatial online control of an object, inferior parietal areas for processing complex object manipulations like tool use and dorsal and ventral premotor areas responsible for the appropriate motor plan and selection of correct hand shape and movements for the action. The pattern of the functionally specialized circuits processing actions shows a dorsal-to-ventral gradient with enhanced involvement of ventral brain areas with increased semantic aspects of an action. While the general control of objects in space recruits brain areas of the dorso-dorsal stream, actions involving more semantic information like the function-specific manipulation of tools, are processed in the ventro-dorsal stream. Importantly, ventral stream areas are not only essential for perception, but also have a key role in action, and interact with the two dorsal pathways. Age-related changes can influence brain processes during real object manipulation. Elderly individuals show over-activations in frontal, parietal and temporal brain areas and compensatory mechanisms in frontal and posterior parietal areas. Such age-related changes in brain networks relevant for actions should be considered in lesion analysis of patients suffering from apraxia.

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PUBLICATIONS

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EIDESSTATTLICHE VERSICHERUNG/AFFIDAVIT

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation „An fMRI-investigation on the neural correlates of Tool Use in young and elderly adults“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation „An fMRI-investigation on the neural correlates of Tool Use in young and elderly adults“ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 24.02.2015

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The author´s contribution to each publication

The neural correlates of Planning and Executing Actual Tool Use.
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The author of this thesis is the first author of the manuscript. M.L.B., A.W., C.S. and J.H. designed research; M.L.B. performed research; M.L.B. and A.W. analyzed research; M.L.B., A.W., C.S. and J.H. wrote the paper.

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Herby confirms the first supervisor the listed contributions of Marie-Luise Brandi to the publications included in this thesis.

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