Human brain networks of auditory attention and working memory

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Abstract

This thesis examines brain networks involved in auditory attention and auditory working memory using measures of task performance, brain activity, and neuroanatomical connectivity. Auditory orienting and maintenance of attention were compared with visual orienting and maintenance of attention, and top-down controlled attention was compared to bottom-up triggered attention in audition. Moreover, the effects of cognitive load on performance and brain activity were studied using an auditory working memory task. Corbetta and Shulman's (2002) model of visual attention suggests that what is known as the dorsal attention system (intraparietal sulcus/superior parietal lobule, IPS/SPL and frontal eye field, FEF) is involved in the control of top-down controlled attention, whereas what is known as the ventral attention system (temporo-parietal junction, TPJ and areas of the inferior/middle frontal gyrus, IFG/MFG) is involved in bottom-up triggered attention. The present results show that top-down controlled auditory attention also activates IPS/SPL and FEF. Furthermore, in audition, TPJ and IFG/MFG were activated not only by bottom-up triggered attention, but also by top-down controlled attention. In addition, the posterior cerebellum and thalamus were activated by top-down controlled attention shifts and the ventromedial prefrontal cortex (VMPFC) was activated by to-be-ignored, but attention-catching salient changes in auditory input streams. VMPFC may be involved in the evaluation of environmental events causing the bottom-up triggered engagement of attention. Auditory working memory activated a brain network that largely overlapped with the one activated by top-down controlled attention. The present results also provide further evidence of the role of the cerebellum in cognitive processing: During auditory working memory tasks, both activity in the posterior cerebellum (the crus I/II) and reaction speed increased when the cognitive load increased. Based on the present results and earlier theories on the role of the cerebellum in cognitive processing, the function of the posterior cerebellum in cognitive tasks may be related to the optimization of response speed.

Tiivistelmä

Tässä väitöskirjatutkimuksessa tutkittiin kuulotarkkaavaisuuteen ja kuulonvaraiseen työmuistiin liittyviä aivoverkostoja mittaamalla tehtäväsuoriutumista, aivojen aktivaatiota ja aivoalueiden välisiä anatomisia yhteyksiä. Ääniin kohdistuvan tarkkaavaisuuden suuntaamista ja ylläpitoa verrattiin kuviin kohdistuvan tarkkaavaisuuden suuntaamiseen ja ylläpitoon, sekä ääniin tavoitteellisesti kohdistettua tarkkaavaisuutta verrattiin niihin tahattomasti kohdistuvaan tarkkaavaisuuteen. Lisäksi tutkittiin kognitiivisen kuormituksen vaikutuksia tehtäväsuoriutumiseen ja aivojen aktivaatioon kuulonvaraisessa työmuistitehtävässä. Corbettan ja Shulmanin (2002) mallin mukaan niin sanottu dorsaalinen tarkkaavaisuusjärjestelmä (päälaen- ja otsalohkon yläosien taaemmat alueet) säätelee tavoitteellista, ”ylhäältä alaspäin” kontrolloitua näkötarkkaavaisuutta, kun taas niin sanottu ventraalinen tarkkaavaisuusjärjestelmä (päälaenlohkon alaosan ja etuotsalohkon sivun alaosan taaemmat alueet) osallistuu näkökohteiden ”alhaalta ylöspäin” käynnistämään tarkkaavaisuuteen. Osoitimme, että myös tavoitteellinen kuulotarkkaavaisuuden suuntaaminen aktivoi samoja päälaenlohkon ja etuotsalohkon yläosien taaempia alueita kun näkötarkkaavaisuuden suuntaaminen. Kuulojärjestelmässä päälaenlohkon alaosan ja etuotsalohkon sivun taaempien alaosan alueiden aktivaation kasvu ei sen sijaan liittynyt vain äänten käynnistämään tahattomaan tarkkaavaisuuteen, vaan myös tavoitteelliseen kuulotarkkaavaisuuden suuntaamiseen. Lisäksi tavoitteelliseen tarkkaavaisuuden suuntaamiseen liittyi myös pikkuaivojen takaosan ja talamuksen aktivaation kasvu, ja etuotsalohkon sisäpinnan alaosa puolestaan aktivoitui ei-tarkkailtavien äänten joukossa esiintyneiden muita hieman voimakkaampien äänten vaikutuksesta. Tämä etuotsalohkojen sisäpinnan alue saattaa osallistua tarkkaavaisuuden puoleensa vetävien äänien merkityksen arviointiin. Tulokset osoittivat myös, että kuulonvaraisen työmuistin tehtävä aktivoi pääosin samoja aivoalueita kuin tavoitteellinen tarkkaavaisuuden suuntaaminen. Kun työmuistitehtävän aikana esiintyvä pikkuaivojen taka-osan aktivaatio kasvoi, koehenkilöiden reaktioajat lyhenivät. Näiden tulosten ja aiempien teorioiden perusteella tämä pikkuaivojen alue saattaa osallistua reaktionopeuden optimointiin kognitiivisessa tehtävässä.

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Kirkkonummi, November, 2009 Juha Salmitaival (a.k.a. Salmi)

List of original publications

Study I Salmi, J., Rinne, T., Degerman, A., Salonen, O., & Alho, K. (2007). Orienting and maintenance of spatial attention in audition and vision: multimodal and modality-specific activations. *Brain Structure and Function*, *212*, 181-294.

Study II Salmi, J., Rinne, T., Degerman, A., & Alho, K. (2007). Orienting and maintenance of spatial attention in audition and vision: an ERP study. *European Journal of Neuroscience, 25*, 3725-3733.

Study III Salmi, J., Rinne, T., Koistinen, S., Salonen, O., & Alho, K. (2009). Brain networks of bottom-up triggered and top-down controlled shifting of auditory attention. *Brain Research*, *1286*, 155-164.

Study IV Salmi, J., Pallesen, K.J., Neuvonen, T., Brattico, E., Korvenoja, A., Salonen, O., & Carlson, S. Cognitive and motor loops of the human cerebro-cerebellar system. *Journal of Cognitive Neuroscience,* in press.

1 Introduction

1.1 Attention and working memory

Attention is a theoretical construct used to describe how relevant information is selected for further processing and how irrelevant information is ignored (*selective attention*; Broadbent, 1958; see also Lachter et al., 2004). Modern theories of attention typically assume that, instead of one bottleneck for the selection of information (e.g., early selection theories, e.g., Broadbent, 1958; late selection theories, e.g., Deutch and Deutch, 1963), attention can affect several stages of processing depending on the current goals and sensory inputs (Johnston and Heinz, 1978; see also Underwood, 1993). Attention may affect information processing via two routes: Salient changes in the environment may trigger attention in a *bottom-up* manner, while attention based on the current goals of behavior can be termed *top-down* controlled attention (Cherry, 1953; see also Wood and Cowan, 1995). Top-down modulations of attention serve to actively maintain attention to a specific target (*maintenance of attention*), such as a particular speaker during a conversation, or to shift attention voluntarily from one target to another (*shifting* or *orienting of attention*; Cherry, 1953; see also Treisman, 1971). In addition, selective attention is thought to play a significant role in ‘higher level’ cognitive processes, such as working memory (Posner and Rorthbart, 2006).

Miller and colleagues (1960) suggested that the storage of a limited amount of information at a time (probably 4-7 units, see Cowan, 2001; Miller, 1956) and the manipulating of this information is based on *working memory* (see also Baddeley and Hitch, 1974). The concept of working memory emphasizes the role of *manipulation of information* in the mind (Baddeley and Hitch, 1974) instead of merely storing information in short-term memory (see Miller, 1956). The manipulation of information in the mind refers to the mental processing (e.g., calculation or transformation) of information contents that are currently in working memory. A working memory model developed by Baddeley and Hitch (1974) suggests that the storage and manipulation of information in working memory is based on two slave systems, a phonological loop and a visuo-spatial sketch pad. The model also suggests that these systems are controlled by a central executive system responsible for directing attention to the relevant contents and coordinating working memory function when, for example, multiple tasks are conducted at the same time. More recent models of working memory (e.g., Barouillet et al., 2007; Cowan, 2001) have attempted to clarify the role of attention in working memory. Cowan (2001) suggested that working memory is not a distinct system, but can be explained in terms of long-term memory and attention (i.e., that working memory is the part of long-term memory that is activated by attention). In Cowan's model, as well as in that of Barouillet et al. (2007), attention causes the bottleneck that limits the capacity of working memory. There is also empirical evidence suggesting a link between working memory and attention (see Awh et al., 2006; Cowan and Morey, 2006). For example, Vogel et al. (2005) showed that participants who could remember more objects from a spatial array also more efficiently excluded irrelevant objects. In other words, working memory and attention seem to be largely overlapping concepts. At the level of brain networks, however, the overlap or segregation of working memory and attention remains largely unclear (see Corbetta et al., 2002).

1.2 Attention-related modulation of brain activity in the auditory and visual modalities

Research on the brain mechanisms of auditory attention has often used the *dichotic listening paradigm* introduced by Cherry (1953). In this paradigm, the participant is presented with different (spoken) messages to the left and right ears, and the task of the participant is to attend to the input delivered to one ear and to ignore the input to the other ear. By applying a dichotic paradigm where series of tones instead of speech were delivered to the two ears during collection of the scalp-recorded electroencephalogram (EEG), Hillyard and colleagues (1973) were the first to show reliably (see Näätänen, 1975) the effect of selective attention on *event-related brain potentials* (ERPs) reflecting time-locked changes in EEG (see *3.1.2*). They reported that ERPs to the to-be-attended tones were negatively displaced at around 100 ms from tone onset at the fronto-central scalp areas in relation to similar tones when they were to be ignored and concurrent tones of different pitch delivered to the opposite ear were to be attended. The authors suggested that this *negative difference* (Nd; Hansen and Hillyard, 1980) was related to the selection of relevant sounds on the basis of their location and pitch.

Auditory attention studies applying EEG (see Alho, 1992), magnetoencephalography (MEG; Degerman et al., 2008; Hari et al., 1989; Rif et al., 1991), positron emission tomography (PET; Alho et al., 1999; Alho et al., 2003; O'Leary et al., 1997; Tzourio et al., 1997; Zatorre et al., 1999), and *functional magnetic resonance imaging* (fMRI;

Degerman et al., 2006) have often applied experimental conditions similar to those used by Cherry (1953) and Hillyard et al. (1973), with the attended and unattended sounds differing from each other in location, pitch, or both. Visual attention, in turn, has often been studied by using the *covert visual attention paradigm* in which the participant fixes his/her gaze at one location and attends to another location. This paradigm was originally developed by von Helmholz (1909). EEG, MEG, PET, and fMRI studies have shown that covert visual attention to a particular location results in location-specific attention-related modulations in the activity of the extrastriate visual cortex (e.g., Corbetta et al., 1993; Heinze et al., 1994; Hopf et al., 2000; Mangun et al., 1998; Martinez et al., 2006; Noesselt et al., 2002; Tootell et al., 1998). Location-specific attention effects occur in specific regions of the visual cortex due to the spatiotopic organization of the visual system that is apparent from the retina to the visual cortex (Tootell et al., 1998). Some visual studies have reported that visual attention to the color, shape, or velocity of the visual stimuli causes modulations of brain activity in distinct extrastriate areas (Corbetta et al., 1990). Electrophysiological recordings in animals suggest that at the cellular level, these attention effects can be observed as specific tunings of the neuronal receptive fields (Moran and Desimone, 1985; see also Fritz et al., 2007).

In the auditory system, there is no evidence for spatiotopic organization in the cortical or subcortical auditory structures of primates or felines (Brugge et al., 2001; Furukawa et al., 2000; Stecker and Middlebrooks, 2003). Instead, spectral auditory information is encoded in tonotopically organized representations in the auditory cortex of non-human primates (Merzenich and Brugge, 1973), canines (Tunturi and Barrett, 1977), and humans (Woods et al., 2009). Tonotopy is apparent throughout the auditory pathway from the inner ear to the auditory cortex (Fettiplace and Fuchs, 1999; Kaas and Hackett, 1998; Lee et al., 2004). Most likely due to the lack of spatiotopic organization in the auditory cortex, auditory attention studies typically show no spatiotopic attention effects (see, e.g., Alho et al., 1994; Degerman et al., 2006; Petkov et al., 2004; Zatorre et al., 1999). Location-specific effects that have been observed in some auditory studies (Alho et al., 1999; Rinne et al., 2008; Woldorff and Hillyard, 1991; Woods et al., 1992) probably reflect the contralateral organization of the auditory pathways (Upadhyay et al., 2007). Consistently, with dominantly contralateral projections from the ears to the left and right auditory cortices, these studies suggest that the attention-related modulations are stronger in the hemisphere contralateral to the location of the attended sounds than in the ipsilateral hemisphere. Based on electrophysiological recordings in non-human primates (Kaas and Hackett, 1999; Rauschecker and Tian, 2000) and felines (Lomber and Malhotra, 2008), researchers have suggested that sound location and sound pitch are processed separately in the auditory cortex. However, related results from human brain imaging studies are not homogenous. Some studies have reported that the attention-related activations for selective attention to sounds in a particular location differ in their auditory cortex distribution from those for selective attention to sounds with a particular pitch (see, e.g., Barrett and Hall, 2006; Degerman et al., 2006; Krumbholz et al., 2007), while other studies have observed no such difference (Degerman et al., 2008; Zatorre et al., 1999).

The aforementioned studies described the structure of the auditory and visual systems, and how this structure is linked to attention-related modulations in the auditory and visual cortices. In addition to the auditory and visual cortices, attention-related modulations are observed in several other brain structures, as theories of attention suggest (Johnston and Heinz, 1978; Underwood, 1993). In the auditory system, for example, attention effects have been observed in the auditory pathway in the inferior colliculus (Rinne et al., 2008) and in the thalamic medial geniculate nucleus (von Kriegstein et al., 2008). In addition, attention affects neuronal activity in at least the prefrontal and parietal cortex (e.g., Alho et al., 1999; Alho et al., 2003; Degerman et al., 2006; Zatorre et al., 1999). Moreover, visual attention has also been shown to affect the thalamus (La Berge and Bushbaum, 1990) and posterior cerebellum (Allen et al., 1997; Le et al., 1998).

1.3 Brain networks involved in top-down controlled and bottom-up triggered attention

Posner (1980) introduced the cue paradigm that may serve to characterize the chronometry of visual attention shifting and its deterioration in neuropsychological patients. In one condition (i.e., endogenous attention condition), the participants are required to focus their attention on a centrally presented visual cue (e.g., an arrow) designating the to-be-attended location. On a trial-by-trial basis, cues are followed by target stimuli either at the to-be-attended location (valid cue) or at the to-be-ignored location (invalid cue). The valid cue is assumed to guide top-down controlled attention, thus facilitating target detection at the cued location, whereas invalid cue is followed by the re-orienting of attention to the location of the target. In another condition (i.e., exogenous attention condition), the cue is presented at the location that is the same as (valid) or opposite (invalid) to the location of the following target. It is assumed that valid cues trigger attention in a bottom-up manner, and that target detection therefore benefits from preceding information at the cue location.

Neuropsychological studies applying the cue paradigm in brain-damaged patients have suggested that the parietal cortex (Posner et al., 1984), thalamus (Rafal and Posner, 1987), and cerebellum (Townsend et al., 1999) are critical for the endogenous or top-down controlled spatial orienting of attention. The results of brain imaging experiments in healthy participants are largely consistent with these results, at least with regard to the cerebro-cortical areas associated with the endogenous orienting of spatial attention (e.g., Corbetta et al., 2000; Hopfinger et al., 2000, for a review see, Corbetta and Shulman, 2002). However, while brain imaging studies have suggested that the top-down controlled spatial orienting of visual attention activates primarily the superior areas of the parietal and prefrontal cortex (Hopfinger et al., 2000), visual hemispatial neglect (a deficit in attention to one side of space, typically to the left hemispace in patients with a right hemisphere lesion) is typically observed in patients with lesions to the inferior parietal or prefrontal cortex (Corbetta and Shulman, 2002).

Based on findings of numerous patient and brain imaging studies, Corbetta and Shulman (2002) suggested that two distinct brain networks are involved in the control of spatial attention (Figure 1): *the dorsal attention system*, consisting of the superior parietal lobule (SPL)/intraparietal sulcus (IPS) and frontal eye field (FEF), is involved in goal-directed or top-down controlled attention shifting, and *the ventral attention system,* consisting of the temporo-parietal junction (TPJ) and inferior/medial frontal gyrus (IFG/MFG), mediates stimulus-driven or bottom-up triggered attention.

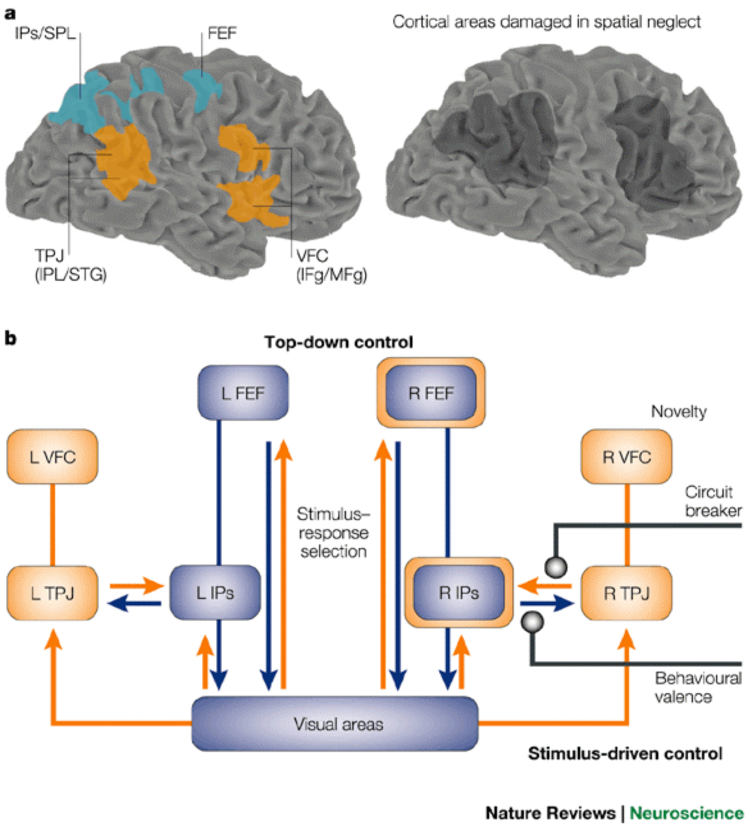

Figure 1. The model of attention by Corbetta and Shulman (2002). *a)* Dorsal (blue) and ventral (orange) frontoparietal networks of attention (left) and regions involved with unilateral spatial neglect (right). FEF, frontal eye field; IPS/SPL, intraparietal sulcus/superior parietal lobule; TPJ, temporoparietal junction (IPL/STG, inferior parietal lobule/superior temporal gyrus); VFC, ventral frontal cortex (IFG/MFG, inferior frontal gyrus/middle frontal gyrus). *b)* The model of top-down controlled and bottom-up triggered attention. The IPS–FEF network is involved in the top-down control of attention (blue arrows). The TPJ–VFC network is involved in bottom-up triggered attention (orange arrows). *Nature Neuroscience,* 3, 201-215. Copyright (2002) Nature Publishing Group. Printed with permission.

FMRI studies of top-down controlled and bottom-up triggered visual attention (e.g., Kim et al., 1999; Kincade et al., 2005; Peelen et al., 2004; Rosen et al., 1999; Serences and Yantis, 2007) support the model by Corbetta and Shulman (2002) with respect to the areas activated by top-down controlled and bottom-up triggered attention. However, this model bears some limitations: (1) Most of these studies (Kim et al., 1999; Peelen et al., 2004; Rosen et al., 1999; Serences and Yantis, 2007) suggest no clear segregation, but an overlap between the brain systems activated by top-down controlled and bottom-up triggered attention; (2) the model is based on studies of visual attention only. Whether the same brain areas are activated by top-down controlled and bottom-up triggered attention in audition and vision remains unknown; (3) the thalamic nuclei and posterior cerebellum are not included in the model, although many studies in brain damaged patients (Hugdahl et al., 1991; Mesulam, 1981; Rafal and Posner, 1987; Townsend et al., 1996, Townsend et al., 1999) and brain imaging in healthy participants (Allen et al., 1997; Gitelman et al., 1999; Le et al., 1998; Yantis et al., 2002) have suggested that these brain areas are important in the control of voluntary attention.

The model by Corbetta and Shulman (2002) is strongly based on results obtained using the cue paradigm. The studies applying this paradigm typically examine brain activity associated with a cue that is followed by a target. As explained above, a centrally presented arrow cue serves to direct attention in a top-down manner towards the to-be-attended location, and a cue presented at the to-be attended location is serves to trigger bottom-up attention. However, both kinds of cues are relevant and require (top-down controlled) attention. One can therefore argue that it is difficult to separate activations associated with top-down controlled and bottom-up triggered attention from each other or from activations associated with other task-related processes, such as the selection of relevant information, using the cue paradigm (Serences and Yantis, 2007). For example, previous ERP studies using the cue paradigm have examined brain activity associated with the spatial orienting of visual attention (Harter et al., 1989; Hopf and Mangun, 2000; Nobre et al., 2000; see also Green et al. 2005). These studies have shown that endogenous cues elicit two successive ERP responses at 200–700 ms after the cue onset. Some have suggested that these responses may reflect activity in the parietal areas related to the orienting of attention (Harter et al., 1989; Hopf and Mangun, 2000) and subsequent modulation of visual-cortex activity (Harter et al., 1989). However, selective attention, anticipation of the target and processing of the cue stimulus may affect these responses. Thus, whether ERPs following an attention-shifting cue actually reflect the orienting of attention or other task-related processes remains unclear. Moreover, ERPs to an attention-shifting cue have been studied mainly in vision while auditory studies have focused on the Nd effects elicited by cued target sounds (Schröger and Eimer, 1993; 1996).

In addition to the cue paradigm, other experimental designs have also been used to study the orienting of attention (see, Shomstein and Yantis, 2006; Vandenberghe et al., 2001; Yantis et al., 2002). For example, Yantis and colleagues (2002) used a modification of a rapid serial visual presentation (RSVP) task. In this task, participants attended to either a letter stream presented to the left of the fixation point or to a concurrent stream presented to the right of the fixation point. In some trials, the participants were to maintain their attention at the current location (maintenance of attention), and in others, they were to shift their attention to the letter stream at the opposite side (orienting of attention). With respect to stimulation, target detection, and demands for selective attention, these trials were similar. Therefore, in contrast to studies using the cue paradigm, Yantis and colleagues (2002) were able to separate maintenance and orienting attention from these other task-related factors that could potentially interfere with the interpretation of results. While the studies using the cue paradigm typically report brain activity in widely distributed brain networks including, in addition to the dorsal and ventral attention systems, for example, the visual and motor cortices (e.g., Corbetta et al., 2000; Hopfinger et al., 2000), Yantis and colleagues reported that the top-down controlled orienting of visual attention is associated with activity in specifically in SPL, MFG, and the superior frontal gyrus (SFG). Later, Shomstein and Yantis (2006) conducted a similar rapid serial presentation study with speech sounds. This fMRI study revealed activations associated with the top-down controlled orienting of auditory attention mainly in the same SPL and frontal areas as in the previous visual study, suggesting that mainly the same brain areas are involved in visual and auditory spatial shifts of attention (see also Wu et al., 2007).

In audition, the distractor paradigm (Schröger and Wolff, 1998) has been used to study the effects of bottom-up triggered attention on behavior and brain activity. In this paradigm, participants are required to press a button in response to each stimulus based on a forced choice detection task (e.g., a shorter or longer tone). Occasionally, task-irrelevant changes occur in these sounds (e.g., their pitch changes during tone-duration discrimination). These task-irrelevant sound changes trigger attention in a bottom-up manner, as indicated by distraction from task performance. Attention and target processing are required for each trial in this paradigm. Therefore, comparison of brain responses to distractor and other sounds reveals brain activity specifically involved in bottom-up triggered attention. Studies using the distractor paradigm (Rinne et al., 2007) or novel sounds among to-be-ignored sounds (Baudena et al., 1995; Dominguez-Borras et al., 2009; Halgren et al., 1995a; Halgren et al., 1995b; Molholm et al., 2005; Rinne et al., 2005), suggest that auditory change detection and subsequent bottom-up triggered attention shifting includes the superior temporal, inferior prefrontal, and inferior parietal cortices (for a review see, Näätänen et al., 2007; see also Yago et al., 2003). Thus, the findings of these studies on auditory change detection and bottom-up triggered attention are mainly consistent with the ventral attention system suggested by the model by

Corbetta and Shulman (2002). However, to date no previous auditory studies have compared top-down controlled attention to bottom-up triggered attention.

1.4 Brain networks involved in working memory

By showing that the activity of neurons in the prefrontal cortex is maintained when non-human primates maintain or manipulate information in the mind, Goldman and Rosvold (1970) provided evidence for neuronal mechanisms of working memory. Subsequent studies have shown that distinct prefrontal neurons are specific to auditory or visual stimulation and even to specific features of the stimuli during working memory processing (Fuster, 1989; Goldman-Rakic, 1987). The role of the prefrontal cortex in working memory is further supported by deficits in working memory tasks in patients with prefrontal lesions (Milner, 1982; see also Müller and Knight, 2006). Based on these findings, research on working memory has traditionally focused on the prefrontal cortex. Later on, however, brain imaging studies have implicated a broader brain network of frontal and parietal areas in working memory (for a review see, Smith and Jonides, 1998).

Braver and colleagues (1997) developed a working memory task for the purpose of brain imaging that enables the parametric manipulation of working memory load while keeping stimulation and motor responses similar. In these *n*-back tasks, participants focus on a sequence of stimuli. In the 1-back task, the participants are instructed to press a response button if the stimulus is the same as the one presented in the previous trial. In the 2-back task, participants are instructed to respond if the stimulus is the same as the one presented two trials before. The increase in working memory load during the *n*-back tasks activates not only the prefrontal cortex, but also the widely distributed brain networks in the superior frontal and parietal cortices, which largely overlap with those activated by the top-down controlled attention studied with the cue-paradigm or RSVP tasks (Carlson et al., 1998; Martinkauppi et al., 2000; for a review, see Smith and Jonides, 1998). Working memory studies, however, typically postulate different functions than do attention studies for these areas: some have suggested, for instance, that the superior parietal cortex contributes to the manipulation of information in working memory, whereas the superior frontal cortex is associated with the monitoring of information that is being manipulated (Champod and Petrides, 2007).

Besides IPS, FEF, and SMA (e.g., Carlson et al., 1998; Martinkauppi et al., 2000), the posterior cerebellum (Chen and Desmond, 2005a,b; Desmond et al., 1997; Hayter et al., 2007; Kirschen et al., 2005) also shows load-dependent activity during working memory tasks. Due to the role of the cerebellum in motor processing (Ito, 2002), it is critical that motor activity be taken into account when studying cerebellar activity associated with cognitive processing. Research shows that with this kind of control working memory tasks partly activate different areas of the cerebellum than do simple motor tasks, such as finger tapping (Desmond et al., 1997; see also Allen et al., 1997). While a simple motor task mainly activates areas of the anterior cerebellum ipsilateral to the hand of response, cognitive tasks cause enhanced activity in posterior cerebellar areas, such as the crus I/II, bilaterally. This dissociation of cognitive and motor cerebellar activity suggests that the cerebellum may contribute to cognitive processing. In keeping with this proposal, studies in non-human primates have shown that the prefrontal and parietal areas involved in working memory are connected to the crus I/II via cerebro-ponto-cerebellar feed-forward projections (Allen et al., 1978; Schmahmann and Pandya, 1989; 1995), and that the crus I/II areas are connected to the prefrontal and parietal areas via cerebello-thalamo-cerebral feedback projections (Middleton and Strick, 1994; 2000). Recent *diffusion weighted MRI* (DW-MRI) studies suggest that the tracts between the cerebral cortex and cerebellum can also be studied in humans based on tracing of the diffusivity of water in the brain (see *3.1.1*, Jissendi et al., 2008; Ramnani et al., 2006).

2 Aims of the study

The aim of the present thesis was to examine the brain networks involved in auditory top-down controlled attention, auditory bottom-up triggered attention, and auditory working memory. Auditory top-down controlled attention was compared with visual top-down controlled attention to reveal if the same brain networks underlie top-down controlled attention in the two modalities (Studies I and II). Auditory top-down controlled attention was also compared with auditory bottom-up triggered attention to reveal the overlap and segregation of the brain networks involved in these processes (Study III). Finally, we studied the brain networks involved in auditory working memory (Study IV) and compared these to brain networks involved in auditory top-down controlled attention (Studies I, II and III).

In more detail, Study I utilized fMRI to examine the brain activity associated with the top-down controlled orienting and maintenance of spatial attention in audition. These activations were then compared to those associated with the top-down controlled orienting and maintenance of spatial attention in vision. Three issues were addressed: (1) Equally demanding (as measured with reaction times and hit rates) auditory and visual orienting and maintenance tasks were designed to compare the modality-specific and multimodal effects of orienting and maintenance attention in audition and vision; (2) in contrast to trial-by-trial studies focusing on rapid activity changes (e.g., those using the cue paradigm; Corbetta et al., 2000; Hopfinger et al., 2000; Kim et al., 1999; Kincade et al., 2005; Peelen et al., 2004; Rosen et al., 1999), possible sustained brain activations during the orienting of attention were also analyzed and predicted that this could reveal activity in the posterior cerebellum and thalamus during the orienting of attention tasks; and (3) the effects caused by differences in sensory stimulation and task demands were minimized (for the methods of Study I, see *3.6.1*) by comparing orienting of attention tasks to maintenance of attention tasks that shared similar sensory inputs and the same number of targets.

In Study II, participants performed during EEG recordings auditory and visual orienting and maintenance tasks similar to those in Study I that applied fMRI. Although previous EEG studies on visual attention have examined ERP effects associated with the orienting of attention (Harter et al., 1989; Hopf and Mangun, 2000; Nobre et al., 2000), they failed to separate these effects from those related to the maintenance of attention. Therefore, whether the reported effects were specifically related to the orienting of attention remains unclear. Moreover, the activity sources underlying these ERP effects are also unclear. Study II compared ERPs and performance during the orienting and maintenance of auditory and visual attention in order to separate orienting-related attention effects from those related to the maintenance of attention. The hypothesis was that comparison of the ERPs to the attended sounds and pictures in the orienting conditions to those in the maintenance conditions could reveal specific effects of orienting of attention on brain activity.

In Study III, brain activity associated with bottom-up triggered and top-down controlled attention in audition was examined with fMRI. Occasional task-irrelevant louder tones among the to-be-ignored and to-be-attended streams of tones served to induce bottom-up triggered shifts of attention. The advantage of using salient sounds instead of exogenous cues to trigger attention in a bottom-up manner is that they can be made task-irrelevant and independent of target events that demand voluntary attention. Therefore, one can probably separate between top-down controlled and bottom-up triggered attention more effectively by using task-irrelevant salient changes than by using exogenous cues followed by targets. Top-down controlled attention shifts were studied by using centrally presented visual cues (arrows) that occasionally guided participants to shift their attention from the left auditory stream to the right one, or vice versa. By using visual cues, the involvement of auditory bottom-up triggered attention during the top-down controlled attention condition was avoided. In Study III, a distinction between bottom-up triggered modulations caused by changes in to-be-ignored and to-be-attended stimulus streams was also made to examine the role of task relevance in bottom-up triggered attention, and the effect of bottom-up triggered attention on top-down controlled attention shifts was studied. Periods of maintained attention with a similar number of targets and with no attention-catching louder tones served as a baseline to eliminate activations associated with selective attention and target processing. Based on previous experiments, the hypothesis predicted that top-down controlled and bottom-up triggered auditory attention activate, at least partly, overlapping areas of the parietal and frontal cortices (Rinne et al., 2007; Watkins et al., 2007).

Study IV examined brain networks activated by non-verbal auditory working memory, and especially the role of the posterior cerebellum in these networks. To reveal the effects of cognitive load increase on performance and brain activity, participants performed working memory tasks of three difficulty-levels during fMRI. In addition, DW-MRI data were collected and tractography analysis tracing the neuronal tracts was performed to investigate the anatomical connectivity within the cerebro-ponto-cerebellar and cerebello-thalamo-cerebral networks. The hypothesis predicted that non-verbal auditory working memory activates networks that overlap with those activated by the orienting of attention (Corbetta et al., 2002). Based on previous studies on verbal working memory (Chen and Desmond, 2005a,b; Desmond et al., 1997) the posterior cerebellum was expected to be activated during auditory non-verbal working memory. Tract-tracing studies in non-human primates (Middleton and Strick, 2000; Schmahmann and Pandya, 1997) suggest that the human cerebellum may be connected with cerebro-cortical areas involved in working memory. Therefore, tractography using the cerebellar activity clusters activated by working memory and those activated by a sensory-motor control task as starting points was performed, and the anatomical connections between these areas and the cerebral cortex were examined.

3 Methods and Results

3.1 Brain research methods used in Studies I-IV

3.1.1 MRI techniques

MRI utilizes the magnetic properties of particles to create a contrast between different structures, such as human brain tissues (Mansfield and Maudsley, 1977). Contrast in structural MRI is typically based on the paramagnetism of hydrogen atoms. The magnetic field of hydrogen atoms aligns with the strong magnetic field (B0 field) in the MRI scanner. In MRI, a radiofrequency (RF) pulse is directed into the magnetic field at a specific frequency, which rotates a magnetic vector of protons against the main magnetic field, and hydrogen atoms absorb energy. When the RF pulse ends, the hydrogen atoms align again with the B0 field and release energy. This energy release (relaxation) has a tissue-specific effect on the MRI signal, which is the basis of the MRI contrast. Spatial location is coded into the MRI signal by using gradient magnetic fields.

In fMRI, the contrast between activated and non-activated tissue is based on changes in the magnetic properties of hemoglobin (Ogawa et al., 1990). The magnetism of hemoglobin decreases in deoxygenation. Increased neuronal energy consumption in activated tissues causes prolific deoxygenation, resulting in a difference between the MRI signals obtained from activated and non-activated tissues. This difference is termed the blood oxygenation level-dependent (BOLD) signal. A major part of the increase in neuronal energy consumption is related to the post-synaptic potentials in the dendrites (Attwell and Iadecola, 2002). Consistently, Logothetis and colleagues (2001) showed that the BOLD signal correlates strongly with local post-synaptic potentials. The MRI technique enables accurate localization of the fMRI signal reflecting these localized metabolic changes, thus providing a spatial resolution of up to a few millimeters. The BOLD signal follows stimulation with a delay of several hundred milliseconds and typically reaches its peak in 4-6 s. Despite the inherent sluggishness of the BOLD signal, fMRI may in some cases serve to separate events in time with a resolution of a few hundreds of milliseconds. In the traditional fMRI-data analysis (Turner et al., 1998), data is fitted to a regression model that is conducted based on timing of the events or blocks of the experiment. Statistical testing is then used to reveal if the signal related to task manipulation differs significantly from the selected baseline. With typical effect sizes (percentage of signal change from 0.1 to 2) the eliciting event has to be repeated for maybe tens of times to get significant effects.

DW-MRI is an application of MRI that serve to determine bundles of white matter tracts between brain regions (Mori and van Zijl, 2002). In DW-MRI, the contrast is based on the anisotropic diffusion of water molecules in brain tissue. Cell membranes restrict diffusion, thus causing stronger molecule movement more parallel rather than perpendicular to the axonal bundles. Diffusion orientation information collected from various angles in DW-MRI may be used to reconstruct the neuronal tracts by using tractography. A DW-MRI signal has a much lower contrast-to-noise ratio than does a structural MRI signal (Behrens et al., 2003). Due to high uncertainties in the signal, probabilistic techniques have proved effective in tracing the neuronal tracts (Behrens et al., 2003). Probabilistic tractography analysis may be performed by first defining specific seed regions (starting points) in the brain, and then determining tracts that connect these seed regions to other brain areas by using a probabilistic algorithm with predefined tracking parameters.

3.1.2 EEG

EEG records the potential difference between two scalp locations as a function of time. EEG measures synchronous activity in large neuronal populations generated mainly by post-synaptic potentials in the dendrites (Rugg and Coles, 1995). As EEG measures electric currents that are directly related to neuronal activity, EEG reflects closely, at a millisecond scale, the time course of activity in synchronously active neuronal populations. Thus, EEG has a far better temporal resolution than the sluggish fMRI signal. The limitation of EEG, in turn, is that the signal does not carry exact information about the source location, which has to be estimated from EEG signals that are recorded with electrodes at the scalp. The inverse problem, as well as attenuation and distortion of EEG signal by tissues between the source and the electrodes, complicates source localization (Picton et al., 1995). However, localization accuracy may be improved by using higher number of recording sites, prior anatomical or neurophysiological knowledge, and advanced source modeling methods.

ERPs are EEG changes time-locked to a certain event, such as the presentation of a sound or picture. However, the eliciting event must be repeated for tens, hundreds or even thousand of times depending on the effect size. The averaging of epochs following each event is required to reveal the signal (i.e., the ERP) and to attenuate "noise" (i.e., EEG activity not time-locked to the event of interest).

3.2 Participants in studies I-IV

In Studies I-IV, participants were healthy right-handed adults with normal hearing, normal or corrected-to-normal vision, and no history of psychiatric or neurological problems. All participants provided their written informed consent prior to testing in accordance with the experimental protocol approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa that also approved Studies I, III, and IV, which applied fMRI. The Ethics Committee of the Department of Psychology, University of Helsinki approved Study II. Table I summarizes the participants in Studies I-IV.

Table 1. Participants in studies I-IV.

Study	N	Females	Age (mean) in years
I	10	5	24-35 (28)
II	13	8	22-36 (28)
III	20	9	21-42 (27)
IV: Exp 1	10	5	22-31 (25)
IV: Exp 2	10	1	23-38 (28)

Eight of the participants in Study I also participated in Study II, and two of the participants in Experiment 1 of Study IV also participated in Experiment 2 of Study IV. In Studies I and III, one participant, and in Study II three participants were rejected from the final analyses based on the specific rejection criteria reported in the articles.

3.3 Stimuli in Studies I-IV

In each experiment, the auditory stimuli were spectrally complex enough to produce strong activations in the auditory cortices (Zatorre et al., 2002). The effective intensity of the tones at the eardrum was about 70 dB SPL. Studies I and II used band-limited (-3 dB bandwidth of the sounds was at 120–180 Hz) normally distributed noise bursts of 100 ms in duration. The center frequency of the noise bursts glided either downwards from 280 to 70 Hz (standards, $p = 0.88$) or upwards from 70 to 280 Hz (deviants, $p =$

0.12). Study III used monoaural iterated rippled noise (IRN) tones (16 iterations, delay 4.1 ms, perceived pitch at 244 Hz) of 40 or 100 ms in duration. In addition, loudness-deviating IRN tones (LDT; 15 dB increment) of 70 ms in duration were occasionally (1.8 % of all tones) presented among the other tones. In Study IV, the auditory stimuli included nine sound combinations (chords) belonging to three different chord categories according to Western tonal music theory ("major", "minor" and "dissonant"), each spanning three frequency levels (high, middle, low) separated by an octave. The major chords played over three octaves consisted of the pitches A, C#, E, A, and C#. Thus, each of the three major chords was played with the same pitches and with a specific frequency (high, middle, or low). Consequently, the major chord was characterized mostly by consonant intervals. The three minor chords played over three octaves consisted of A, C, E, A, and C, thus including the minor third interval. The three dissonant chords, also played over three octaves, consisted of A, Bb, G, Ab, and C, thus including the minor second and several other dissonant intervals. The duration of each chord was 870 ms.

Visual stimuli were presented in Studies I, II, and III. In Studies I and II the visual stimuli consisted of open thin-rimmed "large" and "small" circles presented on a black background for 100 ms. The diameter of the large circle was 4.2° (standard, $p = 0.88$), and the diameter of the small circle was 3.1° (deviant, $p = 0.12$). Central visual stimuli were presented at the center of the screen, and lateralized visual stimuli on the horizontal meridian 5.1° to the left or right of the center of the screen. In Study III, the visual stimulus was a black fixation cross (size 1.5° x 1.5°) surrounded by visual cue that was composed of two arrowheads: one pointing to the left, and the other to the right. During the task blocks, one of the arrowheads was green, indicating the direction where the sounds were to be attended to, and the other was red, indicating the direction where the sounds were to be ignored. It was confirmed before the experiment that all participants could easily distinguish between the green and red colors of the visual cue. During the breaks between the blocks, both arrowheads in the visual cue were black. In all studies, participants fixated on a centrally presented fixation mark during both the tasks and the rest periods between them.

In Studies I and II, the stimuli were presented in independent streams at random 400- to 1400-ms (mean 660 ms) intervals (from offset to onset) between the stimuli within each modality. In Study III, the offset-to-onset interval of the tones varied randomly from 120 ms to 460 ms within each ear, and in Study IV, the offset-to-onset interval of sounds was always 2790 ms.

3.4 MRI acquisition and data analysis (Studies I, III, and IV)

MRI scanning in Studies I and III and in Experiment II of Study IV were performed using a 3T GE Signa scanner. Experiment II of Study IV was performed using a 1.5T Siemens Sonata scanner. Each fMRI study used a head coil around each participants head (also called a birdcage coil). In Studies I and III, fMRI images were collected continuously throughout the experiment. In Study IV (Experiment I), stimulus presentation was interleaved with image acquisition (stimuli were presented during scanner silence). A T1-weighted inversion recovery spin-echo volume was acquired to anatomically align fMRI images of each participant. T1 image acquisition used the same slice prescription as did functional image acquisition, except for a denser in-plane resolution (matrix 256 x 256).

Table 2. Summary of the fMRI and DW-MRI acquisition parameters.

Study	Time of repet. (s)	Slice thickness (mm)	In-plane resolution	Number of slices	Number of vol.
I	2.8	4	3.4 x 3.4 mm^2	28	1050
III	2.0	4	3.4 x 3.4 mm^2	28	1254
IV Exp I	3.66	4	3.5 x 3.5 mm^2	36	896
IV Exp II	10	3	1.88 x 1.88 mm^2	54	128

Data analysis was performed with fMRI Expert Analysis Tool software from the Functional Magnetic Resonance Imaging of the Brain Center (FMRIB) software library (FSL, www.fmrib.ox.ac.uk/fsl, Smith et al., 2004). In order to allow for the initial stabilization of the fMRI signal, the first five to six volumes of each scan were excluded from the analysis. The data were motion corrected, spatially smoothed (Gaussian kernel of 5–7 mm), and high-pass filtered (cutoff 150–300 s). The hemodynamic response was modeled using a gamma (Studies I and IV) or double-gamma (Study III) function. For group analyses, Z-statistic images for each participant were transformed into a standard space (MNI152; Montreal Neurological Institute).

For the time-series analysis, the raw data were motion corrected and high-pass filtered (cutoff 60 s), and the region of interest (ROI) data were transferred to percent signal change values relative to the mean ROI signal across all volumes. The time points (volumes) were then sorted by time relative to the onset of the block, and the ROI time series was linearly interpolated and temporally smoothed using a low-pass Butterworth filter. Finally, the baseline of the ROI time series was set to the mean of the event during a time window of 5–0 s before block onset.

Probabilistic tractography was performed with FMRIB Diffusion Toolkit (FDT) software. The following analysis parameters served for iteration of the tracts: step length = 0.5 mm; number of steps = 2000; number of pathways = 5000; curvature threshold = 0.2 (corresponding to a minimum angle of approximately ± 80º). Moreover, in all analyses, anisotropy constraints implemented in FDT and masks served to exclude non-physiological paths and thresholding to eliminate the most improbable tracts. The results of the tractography analyses were thresholded with a voxel connectivity threshold value of 50 at the individual level. Values between 300 and 4500 were used in the group analysis, depending on the size of the seed, distance between the seed and target region, and lateralization of the tract.

3.5 EEG acquisition and data analysis (Study II)

EEG was recorded at a sampling rate of 500 Hz and a bandwidth from direct current (DC) to 100 Hz. In offline analysis, the auditory and visual events were sampled into epochs beginning 50 ms before and ending 700 ms after each stimulus onset. Mean amplitude over the 50-ms prestimulus period was used as the baseline. Epochs with changes exceeding ± 100 µV were rejected, as were the epochs for the first five stimuli of each stimulus sequence and those followed by a target. For the statistical testing of attention effects on ERPs, electrode matrices were selected from fronto-central locations for auditory ERPs, and from parieto-occipital locations for visual ERPs. These electrode matrices included 3 (anterior to posterior) x 5 (left to right) electrodes for the early responses and 5 (anterior to posterior) x 5 (left to right) electrodes for the late responses. For each electrode, mean amplitudes over 50-ms time windows for the early responses and those over 300-ms time windows for the late responses, centered at the peak latency of the response in the grand-average ERP, were calculated and used in repeated-measures analyses of variance (ANOVAs). Greenhouse–Geisser correction was applied when appropriate, although, the original degrees of freedom are reported together with their correction factor ε.

3.6 Study I: Orienting and maintenance of attention in audition and vision: modality-specific and multimodal activations

3.6.1 Details of the experimental design

Study I utilized fMRI to examine brain activity associated with the top-down controlled orienting and maintenance of attention in audition and vision. The experiment consisted of auditory and visual tasks in which the participants selectively attended to sounds or pictures presented at a central location (maintenance task) or alternated the focus of their auditory or visual attention between opposite lateral locations (orienting task). For details of the experimental design, see Figure 2. During auditory and visual tasks, and rest periods between them, the participants were asked to focus on a small (size 0.7° x 0.7°) yellow fixation cross-presented at the center of the screen. In order to control for sensory and motor activations, similar series of sounds and pictures were delivered, and the same number of responses were required in tasks that were compared to each other. Moreover, auditory and visual stimuli were also presented in unattended locations to decrease the predictability of the next stimulus location and to increase the demands for selective attention. A separate control experiment was conducted to investigate the possible differences in activations related to auditory and visual attention to central vs. lateral locations.

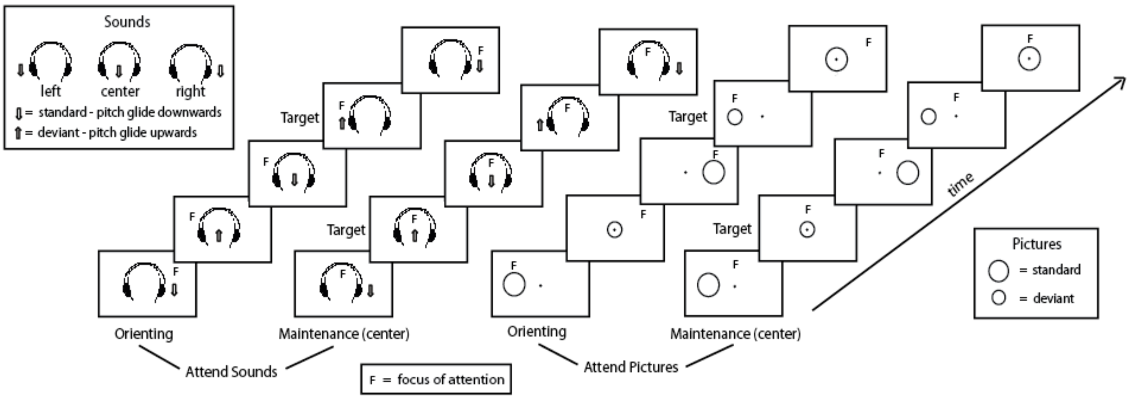

Figure 2. Task design in Studies I and II. Independent sequences of sounds and pictures (open circles) with a duration of 100 ms and an offset-to-onset interval of 400–1400 ms in each sequence were presented in three different spatial locations (left, center, or right). Left and right stimulus locations alternated within the auditory and visual modality. Half of the stimuli appeared randomly in the center location. In the orienting tasks, participants were required to focus their gaze on a fixation cross and to attend to the stimuli presented at the left or right locations (and to ignore the stimuli in the center). After a lateral stimulus had appeared, the participants were to shift their attention to the opposite side and to wait for the next stimulus. In the maintenance tasks, the participants were instructed to attend to the sounds or pictures at the center and to ignore the other stimuli. In the control experiment, the participants maintained their attention either at the left, center, or right. In both experiments, the participants were required to respond to infrequent targets (deviants in the attended modality and at the attended location) in each task. Deviant sounds had an upward frequency glide, and the standard sounds had a downward frequency glide. Deviant visual stimuli were smaller than the standard visual stimuli. F indicates the focus of attention (left, center, or right) on each trial. Study I. Copyright (2007) Springer-Verlag. Printed with permission.

3.6.2 Results

Task performance. There were no significant within-modality differences in hit rates (HRs), false alarm rates (FaRs), or reaction times (RTs) between the orienting and maintenance tasks, or between-modality differences in HRs. RTs were slower in the auditory tasks than in the visual tasks (main effect of modality, $F(1, 9) = 47.7$, $p < 0.001$).

Brain activity in the orienting and maintenance tasks. Auditory orienting and maintenance of attention activated the supratemporal auditory cortices and the inferior parietal and prefrontal cortices more strongly than did the respective visual tasks (Figure 3, top left), whereas only the occipital visual cortex and the superior parietal cortex showed stronger activity during the visual tasks than during the auditory tasks (Figure 3, top right). Auditory and visual orienting of attention tasks activated superior and inferior parietal areas, as well as the middle frontal gyrus, anterior prefrontal cortex, and the posterior cerebellum, when these tasks were compared to the corresponding maintenance tasks (Figure 3, bottom). A comparison between auditory and visual orienting-related activations showed no significant differences ($Z > 1.64$). Moreover, no area showed greater activity for maintenance than orienting tasks in the auditory or visual modality.

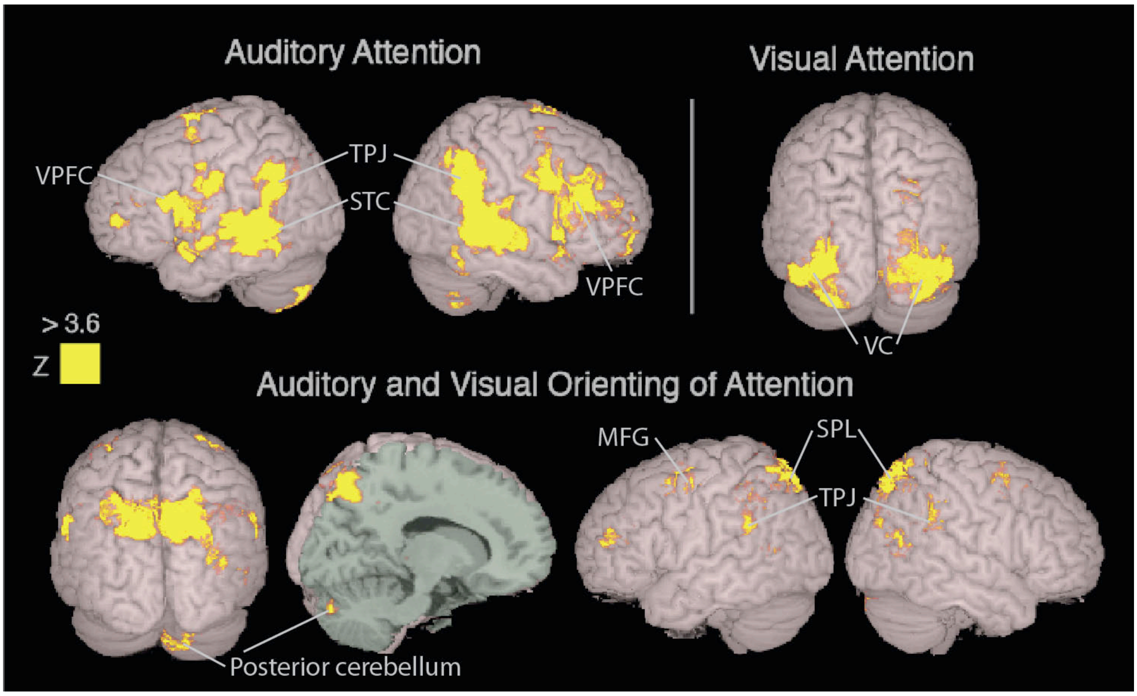

Figure 3. Auditory and visual modality-specific brain activations (top; auditory orienting and auditory maintenance task vs. visual orienting and visual maintenance task), and multimodal orienting-related brain activations (bottom; auditory orienting and visual orienting task vs. auditory maintenance and visual maintenance task). N = 9, voxel-corrected $p < 0.01$; SPL, superior parietal lobule; TPJ, temporoparietal junction; MFG, middle frontal gyrus; VPFC, ventral prefrontal cortex. Medial view is of the right hemisphere. Study I. Copyright (2007) Springer-Verlag. Printed with permission.

These results indicate that mainly the same parietal, frontal and posterior cerebellar areas are activated by the orienting of attention in audition and vision (Figure 3, bottom). Modality-specific differences were found, however, when combined data from both auditory tasks were compared to data from both visual tasks (this comparison shows both the auditory and visual attention-related modulations and modality-specific effects for the orienting and maintenance of attention). In addition to supratemporal auditory cortices, auditory tasks produced stronger activity than did the respective visual tasks in the inferior parietal and prefrontal cortices (Figure 3, top).

3.7 Study II: Orienting and maintenance of spatial attention in audition and vision: an event-related brain potential study

3.7.1 Details of the experimental design

Study II used an experimental design similar to the main condition of Study I. For each modality, there were 12 Maintenance Center conditions, 6 Maintenance Left conditions, 6 Maintenance Right conditions, and 12 Orienting conditions. As the same stimuli and the same target detection task were applied both in Orienting and Maintenance conditions, it was assumed that comparisons of behavioral performance and ERPs to the attended stimuli in the two conditions would reveal effects specifically related to the orienting of attention.

3.7.2 Results

Task performance. No significant differences in RTs, HRs, or FaRs were observed between the Auditory Maintenance Left, Center, and Right conditions. However, RTs in the Auditory Orienting condition were significantly slower than the mean RTs calculated for each participant over the three Auditory Maintenance conditions ($F(1,9) = 24.3$, $p < 0.001$), whereas HRs and FaRs showed no difference between the Auditory Orienting and Maintenance conditions. Nor were any significant differences in RTs, HRs, or FaRs evident between the Visual Maintenance Left, Center, and Right conditions. However, HRs were significantly lower ($F(1,9) = 26.7$, $p < 0.001$) and FaRs higher ($F(1,9) = 30.4$, $p < 0.001$) in the Visual Orienting condition than in the Visual Maintenance conditions. RTs showed no significant difference between the Visual Orienting and Maintenance conditions. As in Study I, RTs were slower in the auditory tasks than in the visual tasks (see article for details).

Auditory and visual ERPs. As Figure 4 (top) shows, ERPs to attended sounds in the Auditory Maintenance Center, Left, and Right conditions showed a negative difference (Nd) over the fronto-central scalp areas in relation to ERPs to similar sounds when participants attended to visual stimuli at the center of the screen (Visual Maintenance Center condition). Attended sounds appearing to the right or left also elicited a significant Nd in the Auditory Orienting conditions in comparison to similar but unattended sounds in the Visual Maintenance Center condition. For the attended sounds at the right, the Nd was stronger in the Auditory Orienting condition than in the

Auditory Maintenance condition at frontal and central midline sites, which resulted in a significant Condition x Electrode interaction (F(14,126) = 1.86, $p < 0.05$, ε = 0.18). In both Auditory Orienting and Auditory Maintenance conditions, the Nds to the sounds at the left and the Nds to the sounds at the right were stronger over the hemisphere contralateral to the location of the attended sounds than over the ipsilateral hemisphere as revealed by repeated-measures ANOVA for mean Nd amplitudes over 150–200 ms from sound onset with factors Condition (orienting, maintenance), Attended location (left, right), Anterior-to-posterior (three electrode rows) electrodes, and Left-to-right electrodes (five electrode columns; Attended location x Left–to–right interaction, F(4,36) = 5.29, $p < 0.01$, ε = 0.15).

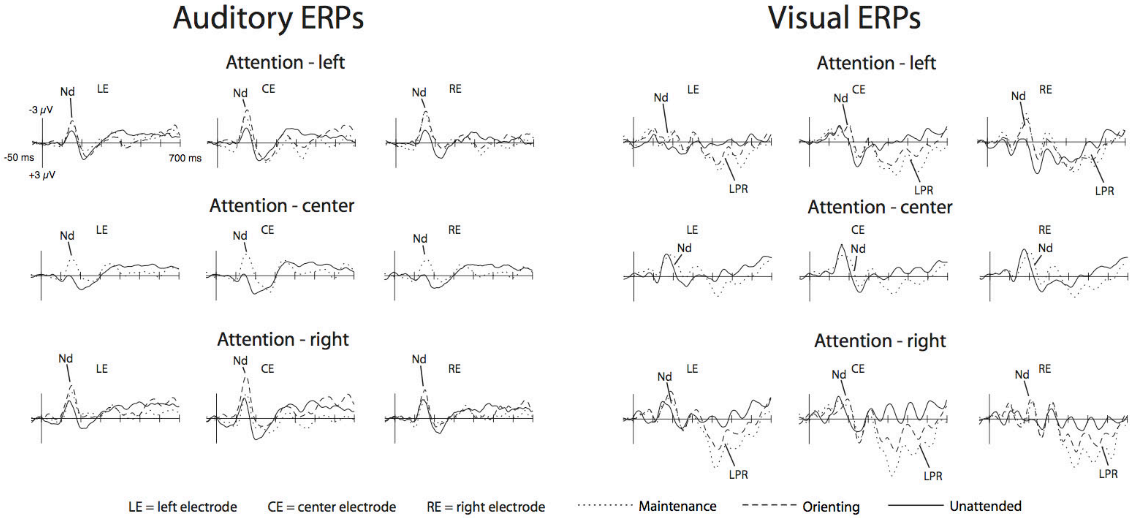

Figure 4. Grand-average (N = 10) ERPs to auditory and visual stimuli (non-targets) at selected electrodes (auditory ERPs: a central electrode corresponding approximately to the Cz location in the 10-20 system; visual ERPs: an occipital electrode corresponding approximately to the Oz location in the 10-20 system). The upper part of the figure shows auditory ERPs, and the lower part shows visual ERPs to the attended and unattended sounds and pictures at the left, center and right in the Maintenance Left, Maintenance Center, Maintenance Right, and Orienting conditions. ERPs to attended sounds showed a negative difference (Nd) in relation to ERPs to similar sounds when the participants attended to visual stimuli. ERPs to attended visual stimuli showed Nd and a late positive response (LPR) in relation to ERPs to similar visual stimuli when the participants attended to sounds. Study II. Copyright (2007) Blackwell Publishing Ltd. Printed with permission.

Attended visual stimuli in the Visual Maintenance Center, Left, and Right conditions elicited an Nd (Figure 4, bottom) as compared to similar but unattended visual stimuli in the Auditory Maintenance Center condition. No significant amplitude differences in the Nds to the lateral visual stimuli were evident between the Visual Maintenance Left or Visual Maintenance Right and Visual Orienting conditions (Figure 4, bottom left and bottom right). In each of these conditions, the Nd began at approximately 100 ms and lasted until 300 ms from stimulus onset. In the Maintenance Left and Right conditions, Nds were stronger over the hemisphere contralateral to the attended location than over the ipsilateral hemisphere. Attended visual stimuli at the right elicited a late positive response (LPR, Figure 4, right bottom) in the Visual Maintenance Right and Visual Orienting conditions relative to similar visual stimuli in the Auditory Maintenance Center condition. The LPR began at around 400 ms, lasted until 700 ms from stimulus onset, and peaked over the parietal areas (Figure 4, right bottom). The LPR was larger for the attended visual stimuli at the right in the Visual Maintenance condition than for similar stimuli in the Visual Orienting condition, as repeated measures ANOVA for mean LPR amplitudes over a 400–700-ms time window (Attention x Electrode rows and columns interaction, $F(24,216) = 1.72$, $p < 0.05$, $\varepsilon = 0.13$) shows. As seen in Figure 4 (bottom), attended visual stimuli at the left also appeared to elicit an LPR at 400–700 ms from stimulus onset in the Visual Maintenance Left and Visual Orienting conditions. However, these LPRs were not statistically significant ($p > 0.1$). Moreover, the LPR amplitudes showed no significant difference ($p > 0.1$) between the Visual Maintenance Left and Visual Orienting conditions.

In contrast to our fMRI findings (Study I), ERPs revealed only minor differences between the orienting and maintenance of attention in audition and vision. The main finding in the auditory modality was that the Nd for the attended sounds at the right was larger in the Auditory Orienting than in the Auditory Maintenance condition (Figure 4, top right), suggesting enhanced activity in the auditory cortex due to increased attention demands. In the visual modality, LPR to the attended visual stimuli at the right, in turn, was larger in the Visual Maintenance condition than in the Visual Orienting condition (bottom right), perhaps due to weaker activity in the extrastriate visual cortex associated with preparation to the stimulus (Harter et al., 1989).

3.8 Study III: Brain networks of bottom-up triggered and top-down controlled shifting of auditory attention

3.8.1 Details of the experimental design

Study III examined brain networks of bottom-up triggered and top-down controlled shifting of attention in audition using fMRI. During the task blocks (the duration of each block was 82 s), the participants were instructed to attend to sounds occurring in the direction of the green arrowhead, to ignore sounds in the direction of the red arrowhead (see Figure 5), and to press a response button when the duration of the attended sounds changed.

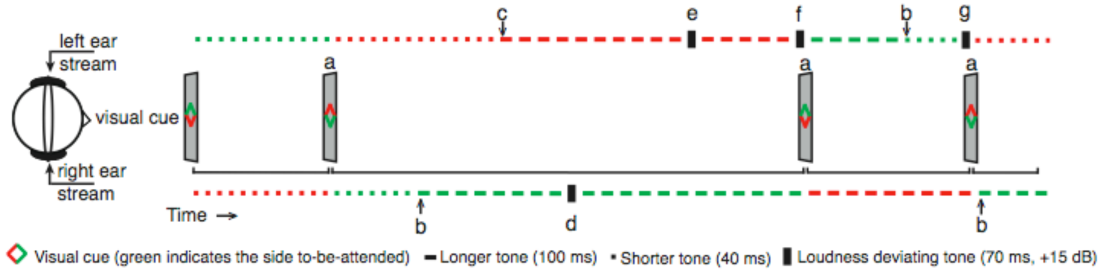

Figure 5. Participants selectively attended to tones at the left or right as indicated by a visual cue comprising green and red arrowheads (pointing in the to-be-attended and to-be-ignored direction) and occasionally shifted their attention between the two tone streams when the cue colors were transposed (a, cue-guided attention shift, CAS). Performance was measured as the reaction times (RTs) of correct responses and the rate of missed responses to a change in duration of the to-be-attended tones (b, target) during sustained attention and after a CAS. Duration changes also occurred on the to-be-ignored side (c, irrelevant duration change). Loudness deviating tones (LDTs) occurred occasionally among to-be-attended and to-be-ignored tones during sustained attention to tones on one side (d, LDT on the to-be-attended side; e, LDT on the to-be-ignored side) or just before a CAS (f, CAS preceded by LDT on the side to-be-ignored before the shift; g, CAS preceded by LDT on the side to-be-attended before the shift). Study III. Copyright (2009) Elsevier B.V. Printed with permission.

When the cue changed (i.e., the green and red arrowheads were transposed), the participants were required to shift their attention accordingly (cue-guided attention shift, CAS). Half of the LDTs occurred 75 ms before a CAS, either on the to-be-attended or to-be-ignored side, and the rest of the LDTs appeared at least 2.8 s after a CAS; that is, they were presented during sustained attention. Target duration changes (from 40 ms to 100 ms or vice versa) could occur during sustained attention to the left or right stream or when participant's the attention shifted (CAS) from one side, where a row of long or short tones preceded the shift, to the other side, where a row of short or long tones, respectively, occurred. Half of the LDTs in the to-be-attended or to-be-ignored stream during sustained attention to one ear, half of the pre-shift LDTs in the to-be-ignored stream and in the to-be-attended stream before the shift, and half of the CASs without LDTs were followed by a target to examine the effect of LDT and CAS on reaction times (RTs) to the targets and the rate of missed responses (Miss%, percentage of missed responses to the targets).

3.8.2 Results

Task performance. During sustained-attention with no LDTs the mean RT to targets was 1161 ms (s.e.m. 47 ms) and the mean miss rate was 5.1% (s.e.m. 1.6%). RTs to the targets decreased (paired samples t-test, t(18) = 6.8, $p < 0.0001$) when a target was preceded by an LDT in the same to-be-attended tone stream, but increased (t(18) = 2.9, $p < 0.01$) when a target was preceded by an LDT in the to-be-ignored stream, as compared with targets during the sustained attention preceded by no LDT. LDTs in the to-be-ignored stream also raised the miss rate (t(18) = 2.9, $p < 0.01$) for the subsequent targets as compared to those during sustained attention preceded by no LDT. For targets preceded by a CAS with no preceding LDT, the mean RT was 1297 ms (s.e.m. 57 ms), which was significantly longer (t(18) = 3.9, $p < 0.001$) than for targets not preceded by an LDT during sustained attention. RTs decreased significantly (t(18) = 3.7, $p < 0.01$) for targets preceded by a CAS, when the CAS was preceded by an LDT in the to-be-ignored stream before the CAS and attended after the CAS as compared with targets following a CAS preceded by no LDT.

Brain activity associated with bottom-up triggered and top-down controlled shifts of attention. Comparison of brain activity associated with these LDT events to brain activity associated with sustained attention without LDTs revealed LDT-related activity in the right TPJ, ventromedial parts of the SPL, posterior parts of the left IFG/MFG, and left FEF/premotor cortex (PMC; Figure 6, top). Comparisons of brain activity following CASs with activity during sustained attention revealed CAS-related activity in the bilateral IPS/SPL, FEF/PMC, TPJ, IFG/MFG, cingulate/medial frontal gyrus (CG/medFG), lateral and ventromedial occipital cortex (OC), and crus I/II of the posterior cerebellum (Post. Cb; center). Thus, both LDTs and CASs activated the ventromedial SPL, left IFG/MFG, left FEF/PMC, and right TPJ. Analysis of activation time-series (Figure 6, bottom) suggested that activity in the right SPL (F(1,18) = 8.6, $p < 0.01$) and posterior cerebellum (F(1,18) = 6.9, $p < 0.05$) ROI was lower when a CAS was preceded by an LDT in the to-be-attended stream before the CAS (green line) as compared to CASs with no preceding LDT (white line), as indicated by repeated-measures ANOVA for mean percentual signal changes with factors Event type (CAS with no LDT, and CAS preceded by an LDT in the to-be-attended stream) and Time from the event onset (4–6, 6–8, and 8–10 s).

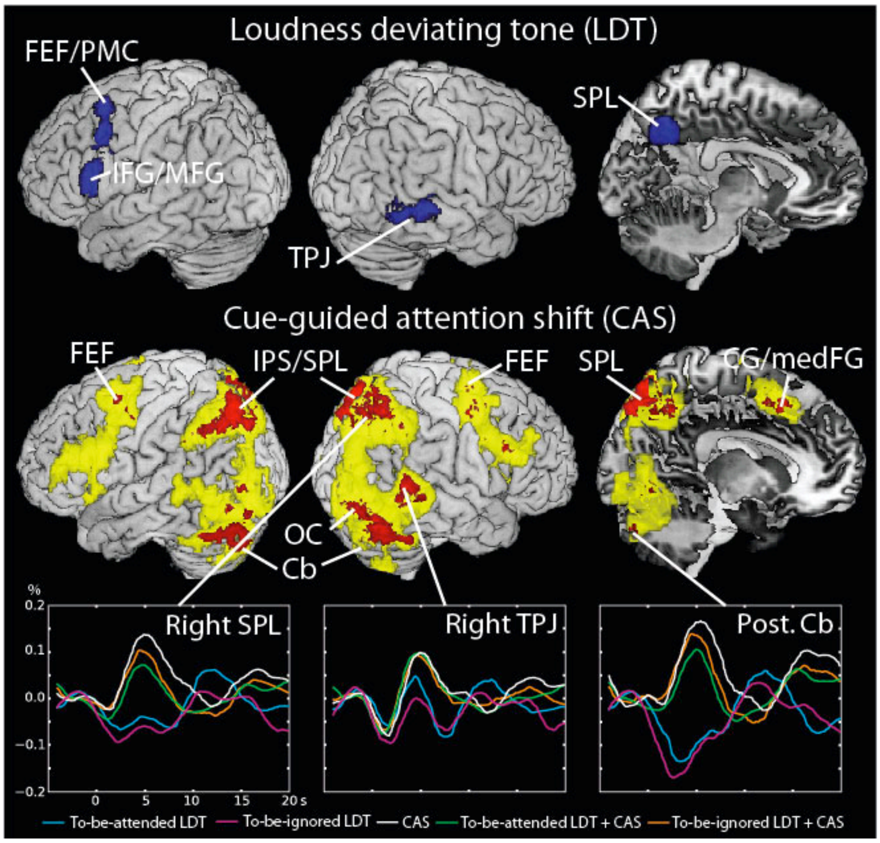

Figure 6. *Top:* Bottom-up influences on brain activity caused by LDTs during auditory sustained attention (blue, Z > 3.0, $p < 0.01$). *Middle:* Top-down controlled CAS contrasted with auditory sustained attention (red, Z > 5.0, $p < 0.01$, and yellow, Z > 3.0, $p < 0.01$). *Bottom:* Activation time-series in the right SPL, right TPJ and posterior cerebellum (Post. Cb) ROIs during different events. Note that the top middle figure shows activity at the posterior temporal cortex. Below the brain surface, however, this activity cluster reached TPJ. Study III. Copyright (2009) Elsevier B.V. Printed with permission.

The effect of locus of attention on bottom-up modulations of brain activity during sustained attention and attention shifting. Brain activity associated with LDTs in the to-be-ignored stream was higher (Z > 1.64, cluster corrected $p < 0.05$) than activity associated with the to-be-attended stream in the ventromedial prefrontal cortex (VMPFC) both during sustained attention and when followed by a CAS (a conjunction of the to-be-ignored vs. to-be-attended LDT contrasts analyzed separately for LDTs occurring during sustained attention and for LDTs preceding a CAS).

Brain activations associated with duration changes in the to-be-attended and to-be-ignored stream during sustained attention. To reveal activity specifically related to the processing of target duration changes occurring in the to-be-attended stream and the processing of similar changes in the to-be-ignored stream, activations were analyzed separately for these changes when they occurred with no adjacent LDT or CAS. These target duration changes activated ($Z > 5.0$, cluster corrected $p < 0.01$) distributed areas of the superior temporal cortex as compared to sustained auditory attention (Figure 7, top, red/yellow). Outside the temporal cortex, target duration changes activated areas of the posterior IFG/MFG, IPS, CG/medFG, left precentral gyrus, and FEF/PMC, bilaterally (top, red/yellow). Activity in the left precentral, central, and postcentral gyrus (contralateral to the hand of response), right IFG and CG/medFG was observed when target duration changes were compared to duration changes in the to-be-ignored stream ($Z > 3.0$, cluster corrected $p < 0.01$, bottom, red). Duration changes in the to-be-ignored stream activated ($Z > 5.0$, cluster corrected $p < 0.01$) areas of STG, IPS, CG/midFG, TPJ, posterior IFG/MFG, and thalamus when they were compared to auditory sustained attention (Figure 7, top, green/yellow). Comparison of brain activity to duration changes in the to-be-ignored and to-be-attended streams, in turn, revealed activation ($Z > 3.0$, cluster corrected $p < 0.01$) in SPL and FEF/PMC bilaterally (Figure 7, bottom, green).

Thus, the present results suggest that bottom-up triggered and top-down controlled auditory attention activates largely overlapping brain areas that correspond to the dorsal and ventral attention systems in vision (Corbetta and Shulman, 2002), as well as in CG/midFG, crus I/II of the posterior cerebellum, and VMPFC. The finding that IPS and superior parts of SPL are activated specifically by top-down controlled attention, whereas the ventromedial SPL is activated by LDTs and to-be-ignored duration changes, suggests that different areas of SPL may play different roles in auditory attention.

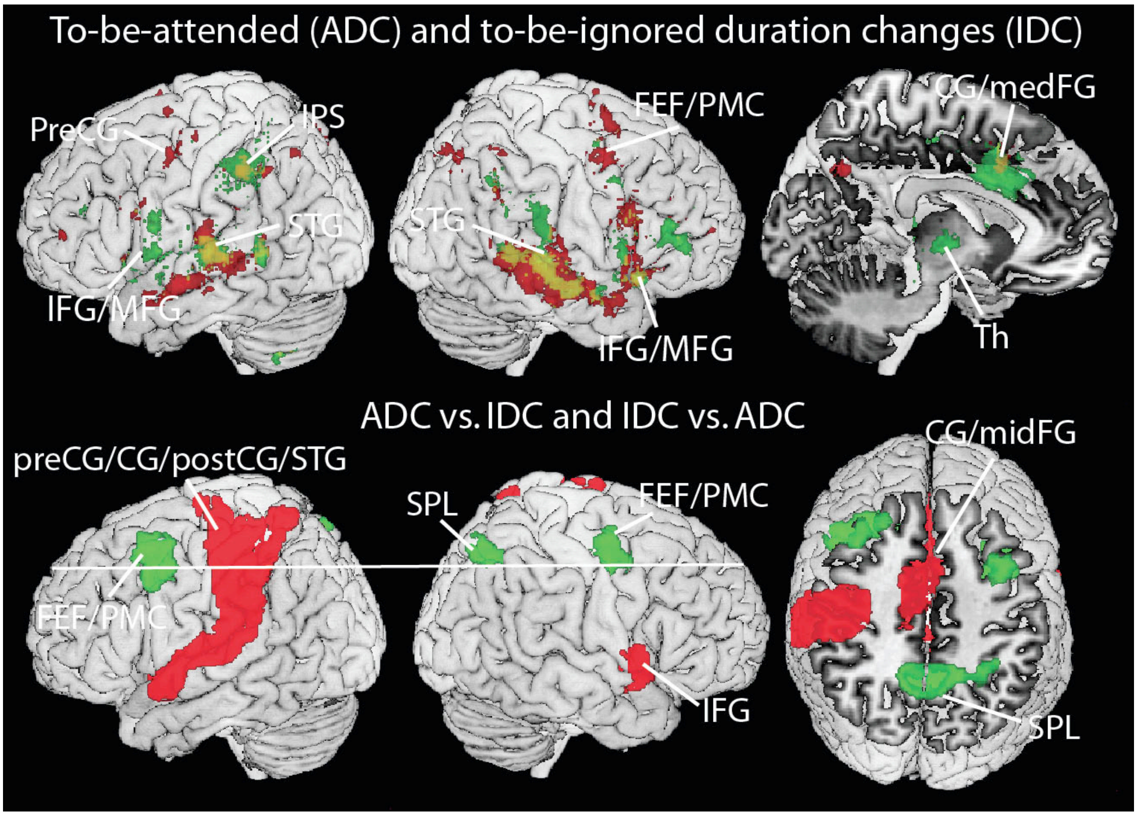

Figure 7. Areas activated (top, Z > 5.0, cluster corrected $p < 0.01$; bottom, Z > 3.0, cluster corrected $p < 0.01$) by duration changes in the to-be-attended (red) and to-be-ignored (green) tone streams during sustained attention as compared to sustained attention with no duration changes (top) or with each other (bottom). Areas that overlap between to-be-ignored and to-be-attended duration changes appear in yellow. The section at the top right is from the medial surface, and the white horizontal line at the bottom left marks the level of the section shown at the bottom right. Study III. Copyright (2009) Elsevier B.V. Printed with permission.

3.9 Study IV: Cognitive and motor loops of the human cerebro-cerebellar system activated by an auditory working memory task and sensory-motor task

3.9.1 Details of the experimental design

Study IV used *n*-back tasks (Braver et al., 1997) during fMRI to examine the brain networks involved in auditory working memory, and specifically the role of the cerebellum in these networks. The participants pressed one of two buttons in response to each sound. In the 1-back task, the participants pressed the left button when a sound was the same as the previous sound (1-back target), and in the 2-back task, when the sound was the same as the one that occurred two sounds back (2-back target). If the sounds were different, they pressed the right button (non-target). In the sensory-motor task, the participants pressed the right button for each sound. Each block began with a 4-s centrally presented written instruction indicating the task. The duration of each task block was 73.2 s (containing 20 trials) followed by an 18.3-s period during which the fixation cross was presented with no sounds. Twelve blocks for each task condition were presented in staircase order (e.g., …sensory-motor, 1-back, 2-back, 2-back, 1-back, sensory-motor, sensory-motor, 1-back, 2-back…). The n-back tasks differed only with respect to the working memory load.

3.9.2. Results

Figure 8 shows the behavioral results of Study IV. An increase in the cognitive load from the sensory-motor task to the 1-back task and further to the 2-back task resulted in longer RTs and higher rates of incorrect responses (IR).

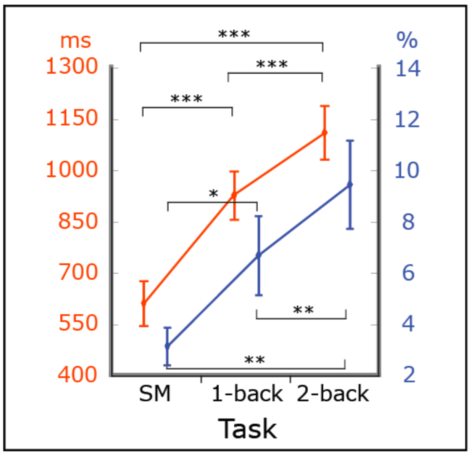

Figure 8. Task performance. An increase in cognitive resulted in longer reaction times (RT, red) and higher rates of incorrect responses (IR, blue). SM = sensory-motor task. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

fMRI results. The across-participants studied 2-back vs. 1-back contrast showed memory-load-dependent activity bilaterally in the IPS/SPL, dPMC, pre-supplementary motor area (preSMA), lateral PFC, basal ganglia, and crus I/II (Figure 9). Moreover, unilateral load-dependent activity was observed in the right lobule VIIB and left lobule VIII of the cerebellum. The contrast between the sensory-motor task and the rest periods revealed activity (Z > 2.5, uncorrected) bilaterally in the motor/somatosensory cortices (MC/SC), medial PFC, STG, posterior cingulate gyrus (PCG), and lobules V/VI of the right anterior cerebellum, as revealed by across-participants analysis.

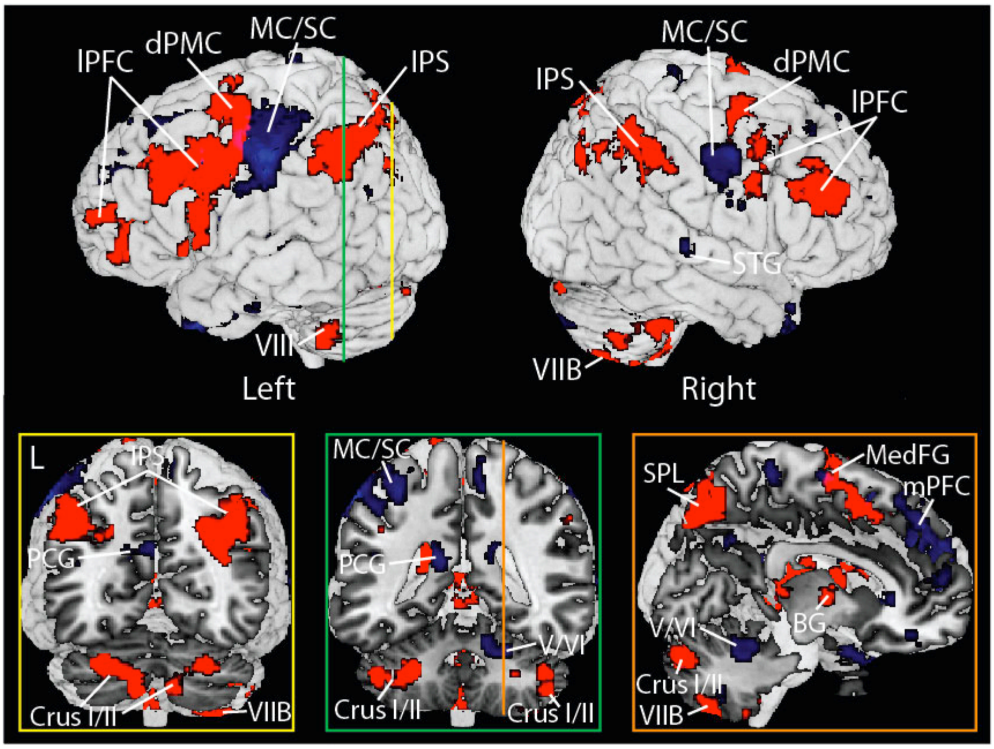

Figure 9. Cognitive-load-dependent (red clusters, 2-back vs. 1-back, Z > 3.1, cluster corrected $p < 0.01$) and sensory-motor (blue clusters, sensory-motor task vs. rest, Z > 2.5, uncorrected) cerebro-cerebellar activity networks across all participants (N = 10). Color-coded vertical lines mark the level of the sections of the images at the bottom. lPFC, lateral prefrontal cortex; dPMC, dorsal premotor cortex; MC/SC, motor/somatosensory cortex; IPS, intraparietal sulcus; STG, superior temporal gyrus; PCG, posterior cingulate gyrus; mPFC, medial prefrontal cortex; SPL, superior parietal lobule; BG, basal ganglia; MedFG, medial frontal gyrus. L = left.

Tractography results. Analysis using the activated cerebellar areas as starting points and pons as the endpoint suggested that the tracts between the pons and the cerebellar areas activated by the cognitive load, especially crus I/II, project mainly via rostral areas of the basilar pons (Figure 10a), whereas the tracts between the pons and cerebellar lobule V/VI that showed sensory-motor activity project mainly via the more caudal nuclei of the pons (Figure 10a).

After determining the subareas of the pons with the highest probability of connectivity to the cerebellum, it was examined which cerebral areas are linked to the activated cerebellar areas via the pons. Probabilistic tractography using crus I/II as a starting point showed tracts that linked the anterior PFC (aPFC), dPMC, M1, SC, and SPL with the cerebellum. When lobule VIIB served as a starting point, tracts connecting lobule VIIB with the aPFC, M1, and dPMC were observed. The lobule V/VI area that was activated by the sensory-motor task showed tracts with the M1 and dPMC. Each of the observed pontine bundles projected via the capsula interna, cerebral peduncle, and dentate nucleus.

Analysis using the cerebellar activity clusters as starting points and the thalamus as an endpoint suggested that the tracts from the activated area in crus I/II were connected mainly to the mediodorsal thalamic nuclei (Figure 10b). Activated areas in lobules V/VI showed tracts connecting these areas mainly with the ventral posterior lateral thalamic nuclei (Figure 10b). Tractography analysis using the activated area in the lobule VIIB as a starting point suggested minor tracts connecting lobule VIIB with the mediodorsal thalamic nuclei, while the activated area in lobule VIII did not have tracts with thalamic endpoints. Crus I/II and lobule VIIB showed tracts connecting these areas via the thalamus with widely distributed areas of the cerebral cortex, including the PFC, SPL, dPMC, and M1. Corresponding analysis using the V/VI activity cluster as a starting point, in turn, revealed tracts connecting only lobule V/VI with the MC/SC, and SPL. The observed cerebello-thalamo-cortical tracts projected from the dentate nucleus to the superior cerebellar peduncles and red nucleus.

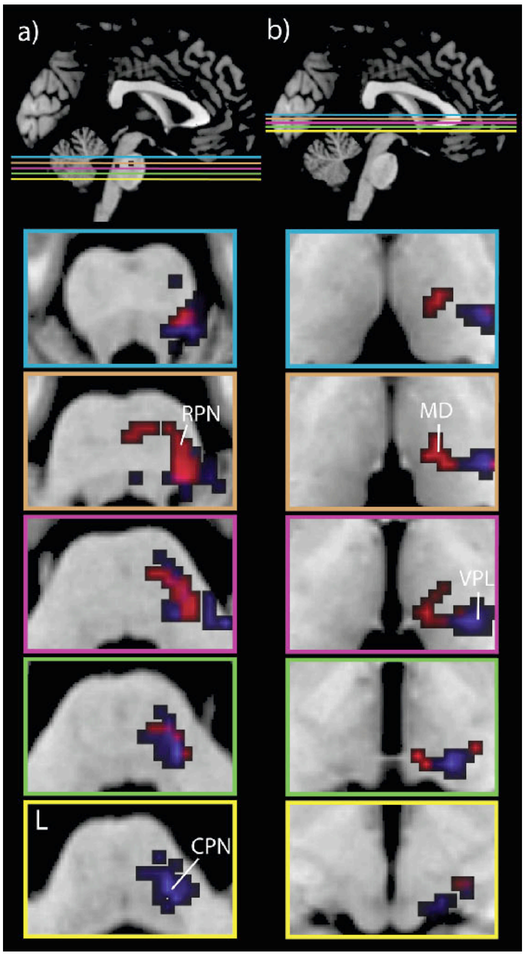

Figure 10. a) Pontine classification of the cerebro-ponto-cerebellar tracts and b) thalamic classification of the cerebello-thalamo-cerebral tracts across all participants (N = 10, the reference image is the individual "Colin" brain of the Montreal Neurological Institute). The positions of the slices in the z-axis are indicated by the colored lines in the sagittal sections of the brain (slices are in order from top-to-bottom). The endpoints of the tracts traced beginning from the right crus I/II activity cluster appear in red, and the endpoints of the tracts traced from the right V/VI activity cluster appear in blue. Areas that include the endpoints of both the tracts traced from crus I/II and lobules V/VI appear in purple. The figure shows ipsilateral and contralateral tracts traced from the crus I/II activity cluster, and only the ipsilateral tracts traced from the lobule V/VI activity cluster (as we were unable to trace the fibers crossing the hemispheres from the activity cluster in lobules V/VI). CPN, caudal pontine nuclei; RPN, rostral pontine nuclei; MD, mediodorsal thalamic nuclei; VPL, ventral posterior lateral thalamic nuclei; L = left.

Correlation between brain activity and performance. Between-participants analysis showed a negative correlation between the load-dependent change in the cerebellar activity and RT. In 2-back vs. 1-back tasks, the correlation between the relative signal change in the left crus I/II and RT was r = -0.735 ($p < 0.05$), and the relative signal change in the right crus I/II and RT r = -0.760, ($p < 0.05$). In 2-back vs. sensory-motor tasks, the relative signal change/RT correlation was r = -0.540, ($p = 0.107$) in the left crus I/II, and r = -0.847, ($p < 0.001$) in the right crus I/II. Activity in the anterior cerebellar ROI showed no correlation with performance in any task condition.

4 Discussion

The present Studies I-IV investigated brain networks involved in attention and working memory. The top-down controlled orienting of attention was compared to the maintenance of attention in audition in studies employing fMRI (Study I) and ERPs (Study II). Study I revealed that the auditory and visual top-down controlled orienting of attention activates similar brain regions. The multimodal brain network activated by the orienting of attention consisted of the SPL/IPS, FEF/PMC, crus I/II of the cerebellum, and the pulvinar nucleus of the thalamus. Modality-specific differences between the orienting and maintenance of attention tasks were observed in the inferior parietal and inferior frontal cortices. These areas were more strongly activated by the auditory tasks than by the visual tasks. Study II further characterized these auditory and visual attention-related modulations. In audition, the top-down controlled orienting of attention was associated with stronger ERP effects (i.e., Nds) than was the maintenance of attention. These Nds were probably generated in the superior temporal cortex (Giard et al., 1988; Rif et al., 1991; Woldorff et al., 1993) and were stronger over the hemisphere contralateral to the attended location. However, ERPs appeared to reflect no orienting-specific activity in the parieto-fronto-cerebellar network observed with fMRI in Study I. Thus, although ERPs provide important temporal information on the selection of attended inputs, they may be less useful for studying the top-down controlled orienting of attention as fMRI. In Study III, bottom-up triggered and top-down controlled auditory attention was studied with fMRI. The results suggested that in audition, top-down controlled and bottom-up triggered attention activates largely overlapping temporo-parietal, superior parietal, and frontal areas. Only IPS, superior parts of SPL, and crus I/II were activated specifically by top-down attention, and VMPFC was specifically activated by bottom-up attention. In study IV, the effects of a cognitive load increase were examined with fMRI in an auditory working memory task. A cognitive load increase in the auditory working memory task (2-back vs. 1-back) resulted in enhanced activity in brain networks that overlapped with those activated by top-down controlled attention in Studies I and III. Study IV also showed that the effect of increasing the cognitive load on the cerebellar crus I/II showed higher activity for shorter reaction times. Moreover, the DW-MRI results showed that crus I/II was connected with those cerebral areas that were also activated by an increase in cognitive load.

4.1 Top-down controlled shifts of auditory attention

The present results suggest that auditory and visual top-down controlled spatial shifts of attention activate mainly the same brain networks (Study I; see also Study III). These results are consistent with those of an earlier neuropsychological study (Farah et al., 1989) and of brain imaging studies that have separately examined visual or auditory top-down controlled spatial shifts of attention (Shomstein and Yantis, 2006; Yantis et al., 2002). It should be noted, however, that auditory and visual top-down controlled attention shifting may be based on different neuronal populations within the same brain area and that these differences may be too small to be detected by neuropsychological tests or non-invasive brain imaging studies. Indeed, neurophysiological recordings in non-human primates suggest that the superior parietal cortex in particular contains mainly neurons that respond to unimodal (visual, somatosensory, or auditory) input (Cohen et al., 2005).

The present results are also in line with those of a wealth of studies conducted in visual modality, suggesting that a network that includes SPL/IPS and FEF/PMC is activated by top-down controlled spatial shifts of attention (Corbetta et al., 1995; Corbetta et al., 2005; Hopfinger et al., 2000; Kim et al., 1999; Kincade et al., 2005; Peelen et al., 2004; Rosen et al., 1999; Shomstein and Yantis, 2006; Serences and Yantis, 2007; Vandenberghe et al., 2001; Yantis et al., 2002). In addition to the top-down controlled orienting of spatial attention, this network is activated by other types of tasks, such as the shifting of attention between two sensory modalities

(Shomstein and Yantis, 2004), the switching of the tasks (Chiu and Yantis, 2009), and working memory (Corbetta et al., 2002; for further information on the overlap of brain networks for attention and working memory, see Chapter 4.3). To cover these divergent findings, Shomstein and Yantis (2006) suggested that this network may be activated by various types of tasks that require the reconfiguration of attention. Recent studies have further examined the specific roles of the superior parietal and superior frontal cortex. These studies suggest that the superior parietal cortex contributes to the binding of information from different sources, which is needed in controlling voluntary attention (Gottlieb, 2007), whereas the superior frontal cortex is involved in the execution of top-down controlled attention shifts (Desmurget et al., 2009; see also Mesulam, 1981). Future studies, would do well to investigate how top-down controlled attention works in more naturalistic situations. For example, studies with cues based on the direction of the another person's gaze suggest that neuronal activity in the dorsal attention system is weaker when attention is shifted according to gaze cues than when it is shifted according to arrow cues (Hietanen et al., 2006; Hietanen et al., 2008). Thus, it is possible that the brain networks involved in shifting spatial attention are somewhat differently activated in conditions that are more naturalistic than those of the present experiments.

In addition to SPL/IPS and FEF/PMC, top-down controlled shifts of spatial attention in audition also activated other brain areas. The results of Studies I and III also suggest that top-down controlled attention in audition activate TPJ and IFG/MFG as well. These results are consistent with those of previous studies reporting activity in these areas during top-down controlled attention or active sound localization (Alain et al., 2008; Alho et al., 1999; Maeder et al., 2001). However, these findings are discrepant with the model of Corbetta and Shulman (2002), thus suggesting that TPJ and IFG/MFG are specifically involved in bottom-up triggered attention. The discrepancy may be due to differences between auditory and visual attention or between the auditory and visual experimental designs, or both. Still, some visual studies report activity in TPJ and IFG/MFG during top-down controlled attention, also (Peelen et al., 2004; Rosen et al., 1999). Finally, Studies I and III suggested that the posterior cerebellum is activated by top-down controlled auditory attention. These results are consistent with those of previous studies reporting on cerebellar activity in attention shifting tasks (Allen et al., 1997; Le et al., 1998). However, many studies of visual top-down controlled attention using the cue paradigm have observed no activity in the posterior cerebellum (e.g., Corbetta et al., 2000; Hopfinger et al., 2000; Kim et al., 1999; Kincade et al., 2005; Peelen et al., 2004; Rosen et al., 1999). The activity of the cerebellum may not have been observed in these studies because they used a trial-by-trial design and because the cerebellum may have shown typically more sustained modulatory activity (Leiner et al., 1991). Study IV further examined the anatomical and functional role of the cerebellum in cognitive processing (see *4.3*).

Although strong effects were found in Study I using fMRI, Study II showed no activity specifically associated with top-down controlled attention. This suggests that attention-related ERPs in this paradigm are not strongly affected by activations of the parieto-frontal network associated with top-down controlled attention. Early negative and late positive ERP components associated with top-down controlled attention shifts in earlier studies (Harter et al., 1989; Hopf and Mangun, 2000; Nobre et al., 2000) were observed in both the orienting of attention and the maintenance of attention conditions in Study II. Therefore, even in conditions demanding top-down controlled orienting attention, the effects of attention on ERPs may be associated with selection of the attended input for further processing after an attention shift rather than with the actual attention shifting. Based on these results, the cue paradigm seems rather limited in ERP studies of top-down controlled attention.

4.2 Bottom-up triggered auditory attention

Study III suggested that auditory change detection and subsequent bottom-up triggered attention activate a brain network that includes TPJ, posterior parts of IFG/MFG, ventromedial parts of SPL, and FEF/PMC. Based on the findings of Studies I and III, none of these regions are activated by bottom-up triggered attention, but also by top-down controlled attention alone. Earlier studies have repeatedly reported the involvement of TPJ and posterior parts of the IFG/MFG in auditory change detection and bottom-up triggered attention (Baudena et al., 1995; Halgren et al., 1995a,b; Knight et al., 1989; Molholm et al., 2005; Woods et al., 1992). Consistent with the present findings, some previous studies have suggested that auditory change detection and bottom-up triggered attention also activate SPL and FEF/PMC (Rinne et al., 2007; Watkins et al., 2006). The activity of SPL and FEF/PMC in Study III, as well as in earlier studies by Watkins and colleagues (2006) and Rinne and colleagues (2007), may be partially explained by the voluntary orienting of attention back to the task after temporary distraction.

In contrast to previous fMRI studies of auditory bottom-up triggered attention, Study III made a distinction between bottom-up modulations in the to-be-ignored and to-be-attended streams. LDTs in the to-be-ignored tone stream were expected to draw attention to this stream, so comparison between LTDs in the to-be-ignored and to-be-attended streams should reflect bottom-up triggered spatial attention shifting. This comparison revealed no changes in the activity of TPJ and IFG/MFG, which may be involved in the bottom-up triggered shifting of spatial attention (Corbetta and Shulman, 2002). Based on the results of Study III, one could propose that, at least in audition, TPJ and IFG/MFG are involved in the detection and processing of changes and not specifically in bottom-up triggered spatial attention shifting. Furthermore, these same results suggest that the relevancy of TPJ and IFG/MFG are not significantly modulated by the relevancy of the event that triggers attention. Comparison of brain activity associated with LTDs in the to-be-ignored and to-be-attended LDTs did, however, reveal activity in VMPFC. Previous studies have suggested that VMPFC is involved in the inhibition of irrelevant stimuli as well as in releasing this inhibition (Bechara et al., 2000; Rolls, 2000; Rule et al., 2002). VMPFC activity observed in Study III in the comparison of processing LDTs in the to-be-ignored and to-be-attended streams may be related to active suppression of the processing of to-be-ignored LDTs during sustained attention as well as to the release of this suppression in order to facilitate attention shifting (to-be-ignored LDT followed by CAS).

4.3 Auditory working memory and attention

Comparison of the results of Study IV with those of Studies I and III suggests that auditory working memory activates brain networks that largely overlap with those activated by auditory top-down controlled attention. On the one hand, the same brain networks may actually be involved in both top-down controlled attention and working memory, as would be suggested by working memory models by Barouillet et al. (2004) and Cowan (2001), which claim that attention and working memory are not distinct but largely overlapping functions. On the other hand, the present experimental designs may have been unable to distinguish between attention and working memory. Because Study IV used a block design that was not intended to control for attention, it is especially likely that the working memory tasks used in this study required top-down controlled attention. Studies using parametric design for manipulating the load of attention and working memory separately would probably help to clarify this issue. A recent study with such an experimental design suggested that at least in the auditory cortex, attention and working memory activates distinct areas (Rinne et al., 2009).

Study IV in particular investigated the role of the cerebellum in working memory. Our results suggest that working memory load increase and sensory-motor processing activate distinct cerebro-cerebellar networks. In keeping with previous studies that used *n*-back tasks (Carlson et al., 1999; Martinkauppi et al., 2000; Rämä et al., 2001), an increase in working memory load activated IPS/SPL, FEF/PMC, and various areas of the prefrontal cortex. In addition, as some previous working memory studies have reported (Chen et al., 2005a,b; Desmond et al., 1997; Hayter et al., 2007; Kirchen et al., 2005), activations in the posterior cerebellum are related to working memory load. Study IV further showed that the load-dependent activity in the cerebellar crus I/II correlated with shorter reaction times. This finding is in agreement with those of previous studies that reported longer reaction times after temporary (Desmond et al., 2005) or permanent (Nixon and Passingham, 2000; Townsend et al., 1999) cerebellar dysfunction.

Consistent with previous studies (Allen et al., 1997; Desmond et al., 1997), Study IV showed that cognitive processing and sensory-motor processing activate specific regions of the cerebellum. These activated regions served as starting points for tractography analysis in examining the segregation of the cognitive and motor loops of the cerebro-cerebellar system, previously studied in non-human primates (see Middleton and Strick, 2000). In line with studies of non-human primates (Brodal, 1978; Kelly and Strick, 2003; Middleton and Strick, 2000; Schmahmann, 1996), Study IV showed that the cerebellar areas activated by cognitive and motor processing are connected with distinct cerebro-cortical regions via specific pontine and thalamic nuclei. Comparison of the fMRI results of Study IV on auditory working memory to those of Studies I and III on top-down controlled attention indicate that the present working memory tasks and attention-shifting tasks activated largely overlapping areas in the posterior cerebellum. The cerebellar activity in working memory tasks may therefore be involved in attention.

4.4 Conclusions

Figure 11 summarizes the main results of Studies I-IV. The figure shows the areas that were activated by top-down controlled attention, bottom-up triggered attention, and working memory in audition. Brain networks activated by top-down controlled attention in audition include the auditory cortex (AC), IPS/SPL, FEF/PMC, DLPFC, TPJ, IFG/MFG, thalamus (pulvinar), and crus I/II of the posterior cerebellum. As earlier studies have suggested, the role of the AC in auditory attention is probably related to the selective enhancement of attended contents (e.g., Petkov et al., 2004). Auditory working memory activates brain networks that largely overlap with those brain networks activated by top-down controlled attention. Based on the present results, the main difference between the brain networks of auditory top-down controlled attention and auditory working memory is that, in contrast to top-down controlled attention, working memory showed no activity in TPJ and IFG/MFG. In addition, working memory tasks did show activity in widespread areas of DLPFC, whereas top-down controlled attention showed relatively little activity in DLPFC. Note, however, that due to completely different task designs and different participants, the results of Studies I and IV should be compared with caution. Auditory change detection and bottom-up triggered attention activated brain networks that include IPS/SPL, FEF/PMC, TPJ, IFG/MFG, and VMPFC. Thus, the DLPFC, thalamus, and crus I/II of the posterior cerebellum were activated by top-down controlled attention and working memory, but not by bottom-up triggered attention, whereas VMPFC was specifically activated by bottom-up triggered attention.

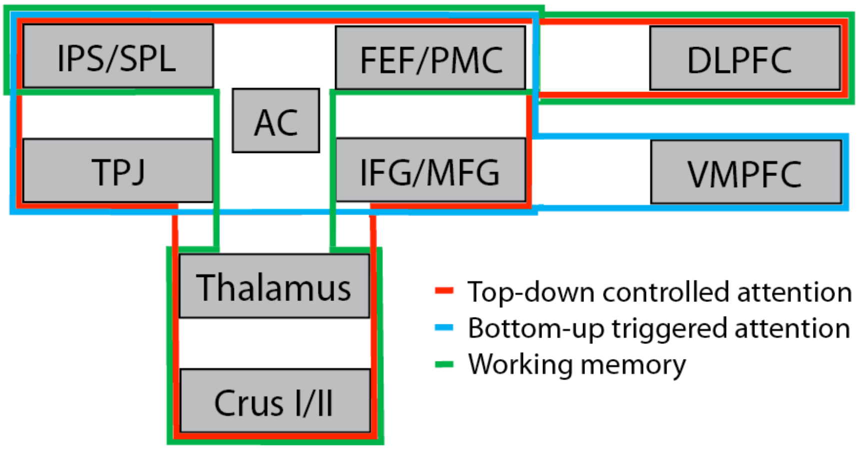

Figure 11. A graphical summary of the results of Studies I-IV. The figure shows the areas involved in top-down controlled attention (red), bottom-up triggered attention (blue), and working memory in audition (green). Colored lines surrounding the boxes outline the areas involved in specific networks. IPS/SPL, intraparietal sulcus/superior parietal lobule; FEF/PMC, frontal eye field/premotor cortex; DLPFC, dorsolateral prefrontal cortex; TPJ, temporoparietal junction; AC, auditory cortex; IFG/MFG inferior frontal gyrus/middle frontal gyrus; VMPFC, ventromedial prefrontal cortex.

By comparing the results of the present and other recent studies, the roles of these areas can be evaluated in even greater detail. (1) Present and previous neuroimaging studies show that IPS/SPL and FEF/PMC are activated by various tasks requiring attention or working memory (Carlson et al., 1998; Chiu and Yantis, 2009; Corbetta et al., 2002; Martinkauppi et al., 2000; Shomstein and Yantis, 2004; Shomstein and Yantis, 2006; Yantis et al., 2002). Studies on attention typically demonstrate rather good control of working memory processing (e.g., Chiu and Yantis, 2009; Shomstein and Yantis, 2004; Shomstein and Yantis, 2006; Yantis et al., 2002), whereas studies of working memory seldom control for attention (e.g., Carlson et al., 1998; Corbetta et al., 2002; Martinkauppi et al., 2000). Moreover, even some working memory studies suggest that the activity in these regions may be involved in attention rather than working memory, as increase in working memory load boost activity in there regions only marginally (Linden et al., 2003). Based on these results, one could propose that IPS/SPL and FEF/PMC are involved mainly in attention and not in working memory. (2) Findings from strictly controlled experiments showing that DLPFC is seldom activated by top-down controlled attention (Chiu and Yantis, 2009; Shomstein and Yantis, 2006; Yantis et al., 2002) suggest that DLPFC may be more involved in working memory rather than top-down controlled attention. This suggestion is supported by neurophysiological studies that propose DLPFC as a key area in working memory (Levy and Goldman-Rakic, 2000). (3) Our results may be insufficient to claim that TPJ and IFG/MFG are involved in top-down controlled attention in audition. The results of Studies I and III, which show activity in these regions during top-down controlled attention, could be attributed to the effect of top-down controlled attention on brain regions (TPJ and IFG/MFG) that may actually be involved in bottom-up triggered attention (see Corbetta and Shulman, 2002). Seldom observed in visual studies, this modulation could be result from stronger dependence on bottom-up triggered attention in audition that in vision (see Kubovy and van Valkenburg, 2001; Mayer et al., 2009), for example, because the auditory signal typically changes more rapidly in time than does the visual signal. (4) The results of Study III, which show activity in VMPFC associated with loudness increments in the stream of to-be-ignored tones, together suggest that VMPFC may be involved in suppression of the processing of irrelevant changes in stimuli as well as in releasing this suppression (see also Rule et al., 2002). (5) Studies I, III, and IV showed activity in the posterior cerebellum during auditory top-down controlled attention and auditory working memory, thus suggesting that the posterior cerebellum is strongly involved in auditory attention and working memory (see also Petacci et al., 2005). The results of Study IV further suggest that the posterior cerebellum may contribute to optimization of the processing speed when the cognitive load increases. In summary, the results of Studies I-IV show that auditory top-down controlled attention, auditory bottom-up triggered attention, and auditory working memory activate distinct but largely overlapping brain networks in the human brain.

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