5 VISUAL WORKING MEMORY FOR NEUTRAL WORDS IN POST-TRAUMATIC STRESS DISORDER

5.1 SUMMARY

Background: This study investigates working memory updating in post-traumatic stress disorder (PTSD). High resolution ERPs were expected to demonstrate activity in visual working memory networks, including the frontal, parietal and posterior temporal regions, during the updating of stimulus content in working memory, at approximately 400-800 ms after relevant stimulus onset. Diminished activity was expected in PTSD patients.

Task Manipulation: Working memory was manipulated by two target detection tasks that only differed in task instructions, as both tasks involved a pseudo-random presentation of red and blue, neutral words. For one task, targets were a specific word in an attended color (a fixed target). In the other task, targets were any repeated words in an attended color (a variable target). Only the latter task requires frequent updating of the target identity in working memory after each non-target attended word. Event-related activity for attended non-target words from each task is compared for both the scalp potential and scalp current density (SCD).

Results: Enhanced component peaks for the working memory updating condition were found in occipital, posterior temporal, parietal and frontal regions. These components were, in order of latency: (a) superior frontal N80 SCD at 80-95 ms, (b) posterior temporal P90 ERP at 90-95 ms and P100 SCD at 105-125 ms, (c) occipital N150 ERP and prefrontal P150 ERP at 145-160 ms, (d) right superior frontal N250 SCD at 230-245 ms and occipital P250 SCD at 240-255 ms, (e) posterior temporal N300 ERP at 290-320 ms, (f) superior parietal P350 SCD at 345-360 ms, (g) superior frontal P400

ERP at 380-420 ms, and (h) superior parietal P500 SCD at 485-515 ms and a P550 ERP at 515-560 ms. The early working memory effects on the N80 SCD and P100 SCD were not observed in PTSD patients. Also, PTSD patients had a delayed frontal P400 ERP and a smaller parietal P550 ERP in the working memory updating condition. The latter findings were clearer in the difference waves, where patients had a smaller and shorter PD550 ERP at 465-595 ms over the superior parietal region and the superior prefrontal region, which was similarly found in smaller PD550 SCD at 550-590 ms over the left superior parietal region and the superior frontal region.

Conclusions: The high-resolution scalp topography of this study provides evidence of abnormal fronto-parietal activity during working memory updating in PTSD. This elementary deficit in neutral information processing has implications for all aspects of cognition and adaptive behavior in PTSD.

5.2 Visual Working Memory in Post-traumatic Stress Disorder

This chapter investigates a specific component of executive functions, working memory updating. Working memory is the short-term storage and manipulation of experience. In essence, working memory is the arena in which immediate sensation is associated with current emotions and actions, as well as previous experience. The validity and efficiency of working memory is critical for adaptive behavior.

This chapter investigates the capacity to update the sensory content of working memory. The capacity to represent experience in working memory is limited and it is important that this content is both accurate and relevant to ongoing action plans. Thus, it is synchronized with sensations that are carefully selected and maintained according to their relevance to goals and action plans. The previous chapter investigated the processes of stimulus selection and evaluation, where the qualities that determine relevant experience did not change. However, as the qualities of relevant experience change, so too must the content of working memory. This chapter investigates the additional working memory activity engaged by changes in the qualities of relevant experience. The processes and possible neural architecture of working memory are considered below, before a specific discussion of the present study.

5.2.1 A Neuropsychological Model of Working Memory

Working memory integrates information about the environment that is obtained from various perceptual and semantic processing systems into a unified, dynamic representation that has temporal and spatial coherence (Baddeley, 1992). Furthermore, working memory provides the facility to integrate this coherent, dynamic representation of the environment with prior knowledge of similar situations so that current goals and activities can be responsive to both a dynamic environment and learning that has occurred in similar situations (Baddeley, 1992).

One of the important functions of working memory is the adaptive maintenance of attention on a limited range of experience, usually relevant to action plans (Miller, 1956; Miller et al., 1960). That is, the processes of working memory effectively establish a highway of information processing that links relevant sensations with previous experiences and appropriate, adaptive actions (Miller & Cohen, 2001). Moreover, working memory may retain information in the absence of stimuli, but if the content of working memory is invalidated or the relationships between sensations, experience and action plans are confused, behavior becomes disoriented (e.g., Fuster, 1991).

There are various types of experience that can enter working memory. Many of them, such as visual and auditory sensation, provide detailed information about the external environment. On the other hand, some sensations provide similar information about the body, such as visceral states and limb positions. In conjunction, the somatic and extra-personal information is used to guide further actions toward intended goal states. To facilitate this process, still more information is available from long-term memory; previous episodic memories that resemble current experiences may be recalled to help clarify expected conditions and outcomes of a situation. All of this information, to some extent, is available to working memory, where it is integrated and associated adaptively, but not all of it can be attended (Miller, 1956; Baddeley, 1992). Only those portions that are particularly relevant to adaptive cognitions and actions are attended during controlled, working memory processing. The ability to control and guide this dynamic flow of associative information processing is the essence of working memory. Disruption of this core component of cognition can lead to distraction and disorientation, and possibly fractionation and dissociation of the person from themselves and their environment - the essence of neurotic and psychotic states.

5.2.1.1 Components of Working Memory

According to Baddeley (1992), working memory consists of several components — a central executive and two slave systems, a phonological loop and a visuo-spatial sketchpad. The phonological loop consists of a transient representation of verbal information and an articulatory control process that provides a facility for subvocal rehearsal. Auditory verbal information has automatic and obligatory access to the phonological loop, but visual verbal or pictorial information must be transformed into subvocal auditory verbal information before entry into the phonological loop. The phonological loop is involved in speech comprehension and it facilitates phonological learning, particularly the long-term memory of novel words. The visuo-spatial sketchpad involves a temporary representation of visuo-spatial information and a control process that refreshes that representation. Sensory content of working memory is derived from primary and secondary sensory cortex, while the control processes of the central executive are related to frontal and parietal association cortex (Baddeley, 1992; cf. Goldman-Rakic, 1996; Ungerleider, Courtney & Haxby, 1998; Smith & Jonides, 1999).

5.2.1.2 Working Memory and Episodic Memory

When information enters working memory it is accessible to conscious awareness and such information automatically activates processes of episodic memory consolidation that are performed by a hippocampal module (Moscovitch, 1992; see also Nadel & Moscovitch, 1998). The hippocampal module is instantiated in a distributed neural network that comprises the hippocampus, the parahippocampal gyrus, the entorhinal and perirhinal cortices, the mamillary bodies and the dorsomedial nucleus of the thalamus, the cingulate cortex, and the fornix (Moscovitch, 1992). Reciprocal connections between these structures of the hippocampal module and the neocortex are activated as the hippocampal module integrates or associates the engrams of the

perceptual modules and semantic systems into a *memory trace* that has an index in the hippocampal module (Moscovitch, 1992). The hippocampal module associates the unique qualities of an experience into an episodic memory that consists of both information of primary interest and its spatio-temporal context (Nadel, 1992; Nadel & Moscovitch, 1998). The hippocampus, in particular, is involved in the encoding of the spatial attributes of episodic memories, "the sparse distributed nature of hippocampal representations exactly fits what is needed to form memories of unique episodes" (Nadel, 1992); other structures in the hippocampal module, such as the perirhinal cortex and the parahippocampal gyrus, are involved in encoding other aspects of episodic memories (Nadel, 1992). Although the content of a memory trace has a precise spatio-temporal association, the process of memory consolidation is not instantaneous — it may take hours, days or months (as indicated by trends in retrograde amnesia; Moscovitch, 1992).

Retrieval of an episodic memory involves activation of an appropriate index in the hippocampal module, which then activates its associated memory trace elements in perceptual modules and semantic central systems so that their engrams can be made accessible to working memory and conscious assessment again (Moscovitch, 1992). This process of distributed activation is called *ecphory* and it is a rapid, automatic process (Moscovitch, 1992). The automaticity of ecphory diminishes the utilization of cognitive resources, but it implies a lack of "intelligent" monitoring, organization, or intervention (Moscovitch, 1992). The hippocampal module has no "insight" into its processes and it is not amenable to conscious intervention, although control of the input and output of the hippocampal module is performed by an executive control system (Moscovitch, 1992). The hippocampal module provides precise spatio-temporal association of engrams, but does not encode relationships among episodic memory traces; the relationships among episodic memories are derived from the output of the

hippocampal module by an executive control system, which is disrupted by frontal lobe damage (Moscovitch, 1992). The precise spatio-temporal qualities of episodes serve to distinguish one episode from another. The development of semantic, associative memory relies on the extraction of similarities and differences among various episodic memories. This process of extraction and comparison requires the "intelligence" of executive systems that interact with the episodic content of the hippocampal module (Nadel, 1992).

> *If the hippocampal circuit can be considered to consist of "raw memory" structures, then the frontal lobes are working-with-memory structures that operate on the input to the hippocampal component and the output from it* (Moscovitch, 1992, p. 262).

5.2.1.3 Executive Systems

Executive systems are associated with frontal lobe networks that have reciprocal connections to diverse cortical and subcortical structures that are vital for the organization of cognition and action. Frontal executive systems access information from sensorimotor perceptual and semantic systems, as well as the episodic memory traces of the hippocampal module (Moscovitch, 1992). The frontal executive systems integrate this information into a dynamic, coherent, and meaningful representation of the internal and external milieu and use it to guide thought, to develop and monitor goals, and to initiate and monitor actions (Moscovitch, 1992).

The operation of frontal executive systems is related to conscious experience and it utilizes the majority of cognitive resources, since most other modules and central systems can operate automatically (Moscovitch, 1992). However, the degree of automaticity of executive functions varies with familiarity with the functional requirements of a situation. Baddeley (1992) has developed a model of the executive control of working memory based on the work of Shallice (1980, 1992; cited in

Baddeley, 1992). The integrative functions of executive control are often an automatic process that has been learned and incorporated in a schematic pattern of activity (Baddeley, 1992). However, when novel or threatening situations arise, executive control processes invoke more cognitive resources to engage in controlled, effortful evaluation and adaptation to the situation (Baddeley, 1992).

> *Action can be controlled at either of two levels, by the operation of a series of existing schemata, or via the Supervisory Attentional System (SAS), which takes control when novel tasks are involved, or when existing habits have to be overridden, for example, when danger threatens* (Baddeley, 1992, p. 286).

5.2.1.4 Summary

Neuropsychology models of working memory propose several components that serve to maintain sensory information for short durations and integrate that information into episodic memory. Furthermore, these components serve to focus attention on relevant information in the process of organizing adaptive action. These models of working memory have evolved from cognitive studies of normal subjects and patients with brain lesions. The recent development of tomographic functional neuroimaging provides the opportunity to investigate working memory in normal subjects. Some of these studies have been informed by prior work on primates. The following section reviews these studies of working memory.

5.2.2 Neuroimaging of Working Memory

A growing body of recent research demonstrates that parallel distributed neural networks instantiate higher cognitive functions, such as attention and working memory (Goldman-Rakic, 1988; Goldman-Rakic, Chafee, & Friedman, 1993).

> *Principles of distributed processing suggest that activity in each node of a network evolves under the continuing influence of activity taking place at*

> *the same time in connected structures - a single pattern of activity arises at virtually a single stroke over a number of interconnected cortical areas* (Goldman-Rakic et al., 1993, p. 453).

Neuroimaging studies reveal that working memory networks comprise distributed, reciprocal connections, involving the prefrontal, parietal, and temporal association regions, in conjunction with limbic, sensory and motor networks (Goldman-Rakic, 1990; LaBerge, 1990, 1995; Fuster, 1991, 1993, 2000; Goldman-Rakic & Friedman, 1991; Posner, 1992; Goldman-Rakic et al., 1993; Posner & Raichle, 1994; Petrides, 1994; McCarthy, 1995; McIntosh, Grady, Haxby, Ungerleider & Horwitz, 1996; Ungerleider et al., 1998; Rolls, 2000; Cabeza & Nyberg, 2000; Barbas, Ghashghaei, Rempel-Clower, & Xiao, 2002). These networks effectively select, enhance or maintain awareness of relevant information and inhibit awareness of irrelevant or distracting information, with the purpose to organize and initiate adaptive actions that satisfy needs or achieve goals (see Desimone & Duncan, 1995; Miller & Cohen, 2001; Miller & Asaad, 2002; Cohen, 2002).

5.2.2.1 Functional Anatomy of Working Memory

The connections of the prefrontal cortex with cortical and subcortical structures mediate the ability to maintain a short-term memory for absent stimulus or affective information (Goldman-Rakic, 1990; Goldman-Rakic & Friedman, 1991; Goldman-Rakic et al., 1993; Fuster, 1991, 1993, 2000; McCarthy, 1995; Petrides, 1996; Ungerleider et al., 1998). Lesions of primate prefrontal cortex have been shown to impair working memory processes. Fuster (1991) describes working memory deficits in delayed matching tasks for temporary lesions of dorsolateral prefrontal cortex in primates. The deficits are largest at 4-16 sec delays and they apply to multimodal and cross-modal stimulus representations. Single unit recordings from the dorsolateral prefrontal cortex indicate a sustained negative potential during the delay period that is

sensitive to both stimulus parameters and contingent response parameters, indicating a role for this cortical region in linking relevant stimulus cues to adaptive responses and maintaining appropriate response sets (Fuster, 1991). A possible mechanism for activation of contingent action involves preparation of motor sets and timely release of the action plans, coordinated by prefrontal connections with subcortical regions (Goldman-Rakic & Friedman, 1991). This influence of the prefrontal cortex on motor activity may arise from modulations of activity in the substantia nigra, caudate, medial dorsal thalamus and motor cortex related to fine motor regulation, with the most likely influence being disinhibition of thalamic nuclei and effective release of motor actions (Goldman-Rakic & Friedman, 1991). Also, the consolidation and automaticity of learned, schematic action patterns may involve the cerebellum, which is often identified in neuroimaging of executive functions (see Cabeza & Nyberg, 2000). Note that prefrontal activity is associated with controlled processing during uncertain or novel circumstances, effecting network interactions that encapsulate the learning required for adaptive action, which may become automatic over time (Passingham, 1996; Miller & Asaad, 2002).

The functional connectivity of the prefrontal cortex is complex, providing opportunity for various interpretations of prefrontal functions (e.g., Goldman-Rakic, 1996a,b; Petrides, 1994, 1996; Barbas et al., 2002; Miller & Asaad, 2002). Given the complexity of prefrontal networks, which are integrated with diverse, distributed cortical and subcortical activity, determination of the precise regional specificity of prefrontal functions has been elusive. Human functional neuroimaging indicates prefrontal activation during working memory processes, although there is considerable variability among studies in their functional specificity (e.g., Paulesu, Frith, & Frackowiak, 1993; Jonides et al., 1993; Cohen et al., 1994; Clarke et al., 1995; McCarthy, 1995; Smith et al., 1995; Awh et al., 1996; Baker, Frith, Frackowiak, &

Dolan, 1996; McCarthy et al., 1996; Salmon et al., 1996; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Belger et al., 1998; Clark et al., 2000; see reviews in Ungerleider et al., 1998; Smith & Jonides, 1999; Cabeza & Nyberg, 2000; Miller & Asaad, 2002).

Prefrontal areas are essential to working memory networks, whereas the concurrent activation of the primary or association sensory cortex is dependent on a particular stimulus modality (Fuster, 1991; McCarthy, 1995; Petrides, 1996; Ungerleider et al., 1998; Barbas et al., 2002). For instance, the occipital cortex is involved in visual working memory, the postcentral gyrus is involved in somatosensory working memory, and the superior temporal cortex, the supramarginal gyri, and Broca's area are involved in auditory and phonological working memory (Baddeley, 1992; McCarthy, 1995; see also Cabeza & Nyberg, 2000; Barbas et al., 2002). Furthermore, sensory activity in these regions may be transformed into another modality, a process that engages the anterior cingulate and dorsolateral prefrontal cortex, as they are involved in the monitoring and transformation of sensory representations from one modality to another to facilitate retention (e.g., Fuster, 1991). For instance, words on a screen may be retained in their visual form in the visual cortex or transformed into phonological or linguistic form to be retained in Broca's area, which is a more effective strategy of retention (Raichle, 1993). It is not entirely clear whether the prefrontal cortex extracts information from sensory and perceptual areas to maintain a local representation or whether the prefrontal cortex links into and maintains a pattern of recurrent activity in sensory and association cortex, although it is clear that reciprocal anatomical connections of sensory and prefrontal regions provide for dynamic network interactions that facilitate working memory processes (Goldman-Rakic, 1990; Fuster, 1991, 1993, 2000; Funahashi & Kubota, 1994; Desimone, 1996; Tanaka, 1999; Miller & Cohen, 2001).

In this regard, it is interesting that a visuo-spatial working memory network comprises activity in the prefrontal cortex that has a similar topographic distribution to the activity in the visual system (Goldman-Rakic, 1990; see also Funahashi, Charles & Goldman-Rakic, 1991; Funahashi & Kubota, 1994; Clarke et al., 1995; Ungerleider et al., 1998; Barbas et al., 2002). The prefrontal cortex contains retinotopic representations of visual spatial locations, with memory for left visual fields represented in the right prefrontal cortex and vice versa (Goldman-Rakic, 1990). Also, there are topographic relationships between the prefrontal cortex and the dorsomedial thalamus (Goldman-Rakic & Porrino, 1985), which also plays a role in working memory, as lesions of the thalamus impair spatial working memory and metabolic activity is enhanced in the anterior and dorsomedial thalamus during spatial working memory tasks (Goldman-Rakic & Friedman, 1991; see also Barbas et al., 2002). In non-human primates, the dorsomedial thalamus contains specific sub regions that comprise a dorsolateral area that projects to the dorsal prefrontal areas (above the principal sulcus), while a ventromedial area projects to ventral prefrontal cortex (below the principal sulcus; Goldman-Rakic & Friedman, 1991). This anatomical specificity may have functional correlates; Wilson, Scalaidhe & Goldman-Rakic (1993) demonstrate that spatial working memory is associated with dorsal prefrontal activity, while working memory for objects is associated with ventral prefrontal activity (see also Funahashi & Kubota, 1994; Pandya & Yeterian, 1996; Ungerleider et al., 1998).

Hence, an important model of prefrontal function differentiates spatial and non-spatial content in working memory. The model proposes that different stimulus content engages specific prefrontal regions that are correlated with the dorsal parietal visual system for spatial processing and the ventral inferotemporal visual system for object processing (see Zeki & Shipp, 1988; van Essen & DeYoe, 1995; Goldman-Rakic, 1996; Ungerleider et al., 1998; Smith & Jonides, 1999; see also Rao et al., 2003). Often the

design of studies to assess this model involves a pseudorandom visual sequence of letters, numbers or objects and a judgment of whether the current event occurred two or three events previously (N-back), with judgments required for the verbal and object qualities of the stimulus (e.g., Cohen et al., 1994; Awh et al., 1996). Performance on these tasks is compared with a control task that requires only simple judgments of whether a current event matches a specific target event, so no working memory storage for the stimulus sequence is required. The functional activations identified in verbal working memory studies are interpreted as executive working memory processes in middle and inferior prefrontal gyri (BA 45 & 46; Cohen et al., 1994) and phonological rehearsal processes in left supplementary and premotor cortex (BA 6) in conjunction with left inferior prefrontal cortex (Broca's area, BA 44; Paulesu et al., 1993; Awh et al., 1996; Salmon et al., 1996), which have been differentiated from verbal working memory storage associated with posterior parietal cortex (BA 40; Awh et al., 1996; Clark et al., 2000; see review of Smith & Jonides, 1999). Furthermore, several studies have used delayed match to sample designs to directly compare spatial and object working memory processes (e.g., Jonides et al., 1993; Smith et al., 1995; Belger et al., 1998), although these tasks do not require the same degree of executive working memory that is elicited by the N-back tasks (Smith & Jonides, 1999). Jonides et al. (1993) identified spatial working memory activity in right prefrontal cortex (BA 47), right posterior parietal cortex (BA 40) and right extrastriate cortex (BA 19). The prefrontal region was implicated in spatial working memory maintenance, while the posterior occipital and parietal regions are related to stimulus processing and storage (Jonides et al., 1993). In comparisons of delayed match to sample for spatial location and faces, Courtney et al. (1998) demonstrated specific activation during the delay periods in bilateral superior frontal sulcus for spatial locations (BA 9, superior and dorsal to the dorsolateral prefrontal cortex [BA 46] and anterior to the frontal eye field

in precentral sulcus [BA 6]), while delay activity for faces was associated with the left inferior frontal cortex. Belger et al. (1998) confirm that visual spatial processing in occipital and dorsal parietal regions engages the right middle frontal gyrus during working memory processing, while visual shape processing in occipital and inferior temporal cortex engages bilateral middle frontal gyri and the left inferior frontal gyrus during working memory processing (see also Smith et al., 1995; McCarthy et al., 1996). Thus, considerable neuroimaging evidence indicates regional prefrontal involvement in domain specific working memory networks.

However, the specific functional relationships of lateral prefrontal cortex may be more complex than the domain specificity model (Goldman-Rakic, 1996; Ungerleider et al., 1998; Smith & Jonides, 1999; cf. Goodale & Milner, 1992; Petrides, 1994, 1996; Owen et al., 1998; Dehaene, Kerszberg, & Changeux, 1998; Cabeza & Nyberg, 2000; Miller & Asaad, 2002). For example, a persuasive 'process' model for prefrontal organization proposes that dorsolateral prefrontal cortex (BA 9 & 46) is active during the manipulation and monitoring of complex working memory content, regardless of the spatial or non-spatial qualities of the content, while the ventrolateral cortex (BA 45 & 47/12) is involved in controlled retrieval and integration of sensory and episodic information to maintain the temporo-spatial coherence of experience, including evaluation and judgments leading to allocating attention to relevant stimulus sequences (Petrides, 1991, 1994, 1995, 1996; Petrides, Alivisatos, Evans, & Meyer, 1993; see also, Rushworth, Nixon, Eacott, & Passingham, 1997; Rushworth & Owen, 1998; Owen et al., 1998; Clark et al., 2000; Cabeza & Nyberg, 2000; Smith, Marshuetz, & Geva, 2002). Furthermore, the dorsolateral prefrontal cortex, involved in monitoring working memory, can be differentiated from the posterior dorsolateral cortex (BA 8) and related frontal eye fields (inferior BA 8 & 6), which are active in the process of guiding visual

search to target stimuli associated with particular visual cues (Petrides et al., 1993; see also Clark et al., 2000).

The role of the dorsolateral prefrontal cortex in monitoring working memory may be associated with similar processes in the medial prefrontal cortex and particularly the anterior cingulate. Anatomical studies indicate that the dorsolateral prefrontal cortex has bidirectional connections with diverse cortical regions, including the anterior cingulate (Goldman-Rakic & Friedman, 1991). The anterior cingulate also plays a role in monitoring working memory; it is active in monitoring ongoing processes for competitive access to limited cognitive resources, allocating attention to coherent content, avoiding distraction and evaluating and regulating contingent response processes (Petrides et al., 1993; Cohen et al., 1994; Posner & Raichle, 1994; Passingham, 1996; Badgaiyan & Posner, 1998; Carter et al., 1998, 2000; Miller & Cohen, 2001; Luks, Simpson, Feiwell & Miller, 2002). Some evidence suggests that the dorsolateral prefrontal cortex may be primarily involved in monitoring the sensory content of working memory, while the anterior cingulate is primarily engaged in resolving contingent response conflicts (see Smith & Jonides, 1999), although recent computational modeling and neuroimaging implicate important interactions of lateral prefrontal cortex and anterior cingulate in working memory and regulation of attention (McIntosh et al., 1996; Miller & Cohen, 2001; Luks et al., 2002). At a broad level, the anterior cingulate is in a position to integrate information from not only dorsolateral prefrontal working memory processes, but also important emotion and episodic memory processes associated with regions of the limbic system, especially the medial temporal cortex, together with the orbitofrontal cortex, and these diverse networks play an important role in orienting responses, which involve inhibition of ongoing action plans and shifting attention toward novel or salient events (Devinsky, Morell, & Vogt, 1995; Halgren & Marinkovic, 1995; McIntosh et al., 1996; Lane et al., 1998; see also Gray,

1982b; Eichenbaum & Otto, 1993; Barbas et al., 2002). Note that these regions of the dorsolateral and medial prefrontal cortex lie in close proximity to supplementary motor areas involved in response preparation and execution (see Baker et al., 1996; Lee, Chang & Roh, 1999; see also Toni, Schluter, Josephs, Friston, & Passingham, 1999).

The functions of the ventrolateral prefrontal cortex can be related to the role of the orbital prefrontal regions in emotion and learning (e.g., Barbas et al., 2002). The orbital prefrontal cortex integrates intrapersonal emotion and visceral states into working memory in the process of monitoring and evaluating action plans. Areas of the limbic system, including the hippocampus and amygdala, provide important visceral information related to rewards and punishments and they have reciprocal connections with prefrontal regions, thereby providing important visceral information into working memory (e.g., van Hoesen, 1982; Oscar-Berman, McNamara & Freedman, 1991; Halgren & Marinkovic, 1995; Rolls, 1995, 2000; LeDoux, 1990, 1995; Dolan, 2000). The limbic system structures, such as the amygdala and hippocampus, are involved in homeostatic regulation processes, including connections with the hypothalamus and regulation of heart rate, blood pressure, respiration, etc (Halgren & Marinkovic, 1995). These limbic system visceral states are important in the generation of emotions and learning. In particular, amygdala and orbitofrontal cortex are involved in generating emotions that are related to primary and secondary reinforcements (pleasure and pain - reward and punishment), which involves evaluation of taste, smell and touch, and the secondary auditory and visual associations with primary reinforcements (Rolls, 1995, 2000; LeDoux, 1990, 1995; Dolan, 2000; Barbas et al., 2002). This evaluation can be made in the context of previous experience, as the connections of the orbitofrontal and ventrolateral cortex with entorhinal cortex facilitate integration of episodic memory with working memory activity and there is evidence that the orbitofrontal cortex is involved in determination of the relevance of episodic memories to current experiences

(Petrides, 1996; Barbas et al., 2002; Bechara, Tranel & Damasio, 2002). Furthermore, the emotional significance of experience is an important determinant of the encoding of episodic memories, so the relations between the orbitofrontal cortex with the entorhinal and associated hippocampal cortex may provide for reciprocal interactions of episodic and working memory content (Eichenbaum & Otto, 1993; Eichenbaum et al., 1996; Eichenbaum, 1997; Tulving et al., 1996; Squire & Zola, 1996; Martin et al., 1996; Dolan & Fletcher, 1997; Rugg, 1998; Strange et al., 1999). Thus, the orbitofrontal cortex is involved in contextual evaluation of the reward or punishment outcomes associated with current stimuli and action plans - it is important in the maintenance of reinforcement expectations and it is often active when confronted with novel, unexpected, and uncertain reinforcement contingencies, where it plays a role in determination of the most beneficial course of action (Damasio, Tranel & Damasio, 1991; Nobre, Coull, Frith, & Mesulam, 1999; Elliot, Dolan & Frith, 2000; Bechara et al., 2002). Furthermore, the orbitofrontal cortex is integrated with other frontal and parietal systems engaged in directing and switching attention, where it plays a role in the inhibition of responses associated with poor outcomes and switching response sets toward more beneficial outcomes (Rolls, 1995, 2000; Elliot et al., 2000; see also Gray, 1982). Many of the psychological propositions of human motivation theories, such as expectancy-valence theory (e.g., Feather, 1982), rely on the integrity of the orbitofrontal cortex and associated working memory processes.

Thus, prefrontal areas contribute to a range of executive processes. An important consensus in the neuroimaging literature is that there is a differentiation of human prefrontal cortex into phylogenetically recent areas, including lateral and dorsal prefrontal regions for analysis of sensory information, and phylogenetically older areas, including ventral prefrontal regions for processing course sensory and visceral information leading to generation of emotion (Goldman-Rakic, 1996; Barbas et al.,

2002; Miller & Asaad, 2002). Also, while studies attempt to differentiate components of spatial and object working memory, it is important to note that these aspects of cognition are integrated in real time. The prefrontal cortex certainly plays an important role in this integration, as it processes diverse spatial and object information from cortical and subcortical regions. In fact, evidence indicates that prefrontal activation is more efficient when processing coherent, integrated spatial and object information than when processing dissociated information (Prabhakaran, Narayanan, Zhao & Gabrieli, 2000; see also Knudsen & Brainard, 1995; Rao, Rainer & Miller, 1997; Miller & Asaad, 2002; Rao et al., 2003).

Important cortical regions other than the prefrontal cortex also serve working memory. Neuroimaging has clarified the functional relationships between prefrontal and sensory association regions, including parietal and temporal regions, which provide not only important unimodal and multimodal sensory information, but also a degree of immediate memory and integration of temporo-spatial qualities into object and semantic constructs (e.g., Petrides, 1994; see also Zeki & Shipp, 1988; LaBerge, 1990, 1995; van Essen & DeYoe, 1995).

The role of the parietal cortex in working memory may be related to integration of multi-modal sensory activity, especially visuo-spatial and somatosensory information. Spatial working memory processes, among other higher cognitive processes, involve considerable interaction between the parietal cortex and prefrontal and premotor areas (including the frontal eye fields), as these regions integrate extrapersonal and intrapersonal spatial information from visual, auditory, somatosensory and vestibular sensory systems with eye movements and intentional action plans (Jonides et al., 1993; Petrides et al., 1993; Clarke et al., 1995; Smith et al., 1995; Smith, Jonides, & Koeppe, 1996; Andersen, Snyder, Bradley, & Xing, 1997;Wise, Boussaoud, Johnson, & Caminiti, 1997; Belger et al., 1998; Corbetta et al., 1998; Culham et al., 1998;

Ungerleider et al., 1998; Owen et al., 1998; Iwamura, 1998; Colby & Goldberg, 1999; Decety & Grezes, 1999; Eskandar & Assad, 1999; Graziano, 1999; Zangaladze, Epstein, Grafton, & Sathlan, 1999; Prabhakaran et al., 2000; Barbas et al., 2002). It should be noted that studies of primate activity during delayed match to sample tasks indicate a dissociation of dorsolateral prefrontal cortex and parietal cortex, where both spatial and non-spatial performance is impaired by lesions of dorsolateral prefrontal cortex, while lesions of the parietal cortex disrupt spatial working memory, but they do not disturb performance of a color matching task (Fuster, 1991). Furthermore, human studies have dissociated prefrontal executive functions, which monitor and manipulate working memory, from posterior parietal and inferior temporal systems for maintaining stimulus representations (e.g., Owen et al., 1996; Petrides, 1996; Belger et al., 1998). The executive systems of the prefrontal cortex may gain access to visuo-spatial processing via the cortico-cortical connections with the parietal cortex and, in turn, the dorsal visual processing system (e.g., Büchel & Friston, 1997). These findings link the parietal cortex to visuo-spatial and somatosensory integration in working memory, whereas non-spatial visual processing is related to the ventral visual pathways, which have been implicated in non-spatial working memory processes (e.g., Fuster, 1993; Owen et al., 1996, 1998; Belger et al., 1998).

However, there is human neuroimaging evidence for parietal involvement in non-spatial working memory tasks (e.g., Awh et al., 1996; Smith & Jonides, 1999; Prabhakaran et al., 2000; Clark et al., 2000; see also Dolan et al., 1997; Clark et al., 2001; Moores et al., 2003). The inferior and posterior parietal cortex (BA40) is implicated as a phonological store and general multimodal sensory convergence region, providing a capacity for integrated auditory and visual perception (Awh et al., 1996; Dolan et al., 1997; Clark et al., 2000). It is important to note that spatial and object perceptions are integrated, which involves parietal and inferior temporal interactions

(Prabhakaran et al., 2000; Rao et al., 1997, 2003). Furthermore, both the ventromedial and dorsolateral prefrontal cortex and the parietal cortex are linked with inferior temporal cortex and medial temporal areas (including the entorhinal cortex, parahippocampus and hippocampus) during object perception, attention orientation, working memory and episodic memory (Goldman-Rakic, 1990; Goldman-Rakic & Friedman, 1991; Petrides, 1991; Eichenbaum & Otto, 1993; Halgren & Marinkovic, 1995; Knight, 1996; Dolan et al., 1997; Dolan & Fletcher, 1997; Iijima et al., 1996; Fernandez et al., 1999; Daffner et al., 2000, 2003; Barbas et al., 2002; see also LaBerge 1990, 1995). Thus, it is likely that parietal cortex is involved in both spatial and non-spatial working memory tasks, although the precise areas of parietal cortex and the associative networks engaged may vary for these modalities.

Non-spatial, object working memory has been related to ventral extrastriate visual processing, involving the occipito-temporal and inferior temporal cortex (Fuster, 1993, 2000; cf. Desimone, 1996; Belger et al., 1998; Owen et al., 1998; Ungerleider et al., 1998; Prabhakaran et al., 2000; Buckner, Koutstaal, Schacter & Rosen, 2000; Cornette, Dupont, Bormans, Mortelmans, & Orban, 2001). The maintenance of activity in prefrontal cortex during delayed match to sample may provide the basis for top-down modulation of extrastriate visual activity that is relevant to ongoing action plans (Desimone, 1996; McIntosh et al., 1996). Experiments demonstrate that lesions of either the prefrontal cortex or inferotemporal cortex can impair performance on visual non-spatial working memory tasks and examination of single unit recordings indicates that interactions of these regions facilitate the retention of absent stimulus information relevant to action plans (Fuster, 1993, 2000). For example, inferotemporal networks respond preferentially to stimulus colors both during stimulus display and also during the delay periods of delayed match to sample tasks (Fuster, 1993; McIntosh et al., 1996). Furthermore, some units of these networks exhibit patterns of activity indicating

a specific role in retention, as they were inhibited during stimulus display, but active during the delay period, while other units exhibited specific responses to sensory cues and no activity during the delay periods (Fuster, 1993; cf. Begleiter, Porjesz & Wang, 1993; McIntosh et al., 1996; Desimone, 1996; Ungerleider et al., 1998; Owen et al., 1998). It is important to note that the inferotemporal cortex participates in a network of prefrontal and limbic systems, including anterior cingulate and medial temporal cortex, in the encoding and maintenance of visual object content, although prefrontal regions may dominate these interactions with greater retention intervals (e.g., McIntosh et al., 1996). Thus, there is evidence for local inferotemporal networks for acquisition and retention of non-spatial visual information, which interacts with the prefrontal cortex to effectively integrate relevant visual information with working memory and action plans.

5.2.2.2 Temporal Dynamics of Working Memory

Tomographic neuroimaging studies can illustrate the brain regions engaged during working memory processes, but they generally fail to provide high temporal resolution and therefore cannot investigate the dynamics of activity in working memory networks. A better measure of these dynamics requires electrophysiology, including depth electrodes, EEG and MEG.

Recent work on neural network dynamics investigates the temporo-spatial coherence of electrophysiology signals (see Klimesch, 1999; Basar, Basar-Eroglu, Karakas, & Shurmann, 2000; Varela, Lachaux, Rodriguez, & Martinerie, 2001). This research demonstrates synchronized activity in local cortical networks involved in sensory perception or binding, where the local sensory networks engage in processing interactions in the high-frequency gamma band (40 Hz; e.g., Singer & Gray, 1995; Treisman, 1996; Miltner, Braun, Arnold, Witte & Taub, 1999; Rodriguez et al., 1999; see also Pulvermüller, Keil & Elbert, 1999). Furthermore, short-range cortical networks, involving temporal and parietal association areas, appear to be synchronized

at lower frequencies, in the beta band (13-18 Hz) during multimodal encoding processes (von Stein et al., 1999). Recent studies of working memory indicate that EEG signals at the frontal and posterior regions have coherent oscillations in the theta frequency band (4-7 Hz; Sarnthein, Petsche, Rappelsberger, Shaw & von Stein, 1998; see also Yordanova & Kolev, 1998; Jensen & Tesche, 2002). It is proposed that these low frequencies serve to integrate the activity across the relatively long-range network connections of prefrontal and posterior association areas. Moreover, there is modeling evidence that these long-range frontal and posterior networks engage not only cortico-cortical connections, but also medial temporal and hippocampal connections (McIntosh et al., 1996; see also Büchel & Friston, 1997; Tesch & Karhu, 2000). The medial temporal region, including hippocampus and parahippocampal cortex, is known to generate theta oscillations that play an important role in the integration of prefrontal and posterior association cortex during working memory and episodic memory processes (Eichenbaum & Otto, 1993; Klimesch, Schimke & Schwaiger, 1994; Iijima et al., 1996; Sarnthein et al., 1998; see also Nadel & Moscovitch, 1998; Stern et al., 2001). A general model of these functional relationships proposes that cortex and parahippocampal interactions serve to integrate and sustain multimodal and semantic representations, while the hippocampus compares and organizes information in episodic memory (see Eichenbaum & Otto, 1993; Eichenbaum et al., 1996; Goldman-Rakic, 1996; Martin et al., 1996; Dusek & Eichenbaum, 1997; Nadel & Moscovitch, 1998; Strange et al., 1999; Lisman & Otmakhova, 2001; Strange & Dolan, 2001; Stern et al., 2001; Vinogradova, 2001; see also Gray, 1982, 1988). Finally, evidence indicates that synchronized oscillations integrate distributed neural assemblies during specific stages of information processing and this coherent neural mass action gives rise to the component activity in scalp recorded potentials (see, Lehmann & Skrandies, 1984; Basar et al., 2000; Rennie, Robinson & Wright, 2002; Wright et al., 2003). For

example, EEG evidence indicates that theta frequencies are related to working memory and the scalp recorded P3 ERP (Yordanova & Kolev, 1998; Jensen & Tesche, 2002).

The temporal dynamics of working memory have been studied with ERPs and some of this evidence is related to the P3 ERP component. Among many attributes of stimulus modulation investigated in P3 ERP studies, the P3 has been shown to be sensitive to working memory loads (Magliero et al., 1984; Leuthold & Sommer, 1998; Pritchard et al., 1999). Working memory processes have been associated with enhanced positive activity at parietal regions (P3b; Rösler, Borgstedt & Sojka, 1985; Clark et al., 1998; see also Donchin & Coles, 1988).

For example, Rösler et al. (1985) employed a task that allowed investigation of stimulus and response updating processes. They used a priming paradigm that involved interpreting one of four visual symbols (/, \, *, #), where the first and third symbols indicate a right finger response and the others indicate a left finger response. Note that there is a degree of concrete (/, \) vs. abstract (*, #) representation in these stimuli. An initial stimulus presentation primed a specific response expectation. If the following event stimulus was identical to the prime, no stimulus or response updating occurred. On the other hand, if the event stimulus was different from the prime, it elicits an update of the stimulus representation and if the new stimulus requires a different response, it also elicits an update of the response representation. For example, '/' followed by '/' elicits neither stimulus nor response updating, '/' followed by '*' elicits stimulus updating but not response updating, while '/' followed by '\' elicits both stimulus updating and response updating. Rösler et al. (1985) demonstrate that updating sensory representations is related to greater parietal P3b and positive slow wave amplitude, while updating responses has no impact on these potentials. Furthermore, their study shows that updating sensory information elicits greater P3b activity, indicating greater

resource allocation when the new information contains abstract, symbolic rather than concrete content.

Recently, high-resolution ERP studies have clarified the scalp topography and cortical sources of working memory activity. For example, Gevins et al. (1996) report a high-resolution cortical source estimation study that compared spatial and verbal working memory. Working memory was manipulated by a continuous comparison of the current stimulus with a working memory representation of the third most recent stimulus (a "three-back" task). This required continuous updating of a sequence of three stimulus representations, with an effective retention delay of 13.5 seconds. Activity in this task was compared with a control task that only required detection of a match with the first stimulus in a block, so the target event was a constant, as in a conventional oddball task. The verbal and spatial components of the task were manipulated in different task blocks, with task performance dependent on matching either single letters or their location on the screen (determined by 12 radial locations on two concentric rings). In all conditions, subjects were required to respond to indicate whether the current stimulus is a match or not, so the response requirements were effectively constant. Their results for the non-matching stimuli, which elicit the greatest working memory updating activity, demonstrate working memory activity in a positive vertex potential at 200 ms and further positive potentials over the frontal and parietal areas between 300-900 ms after stimulus onset (Gevins et al., 1996). In particular, working memory was associated with a series of positive ERPs: one at 300 ms over the dorsolateral frontal areas (larger over the right hemisphere), another at 450-600 ms over the left superior and middle frontal gyri, and another at 600-900 ms over bilateral supramarginal gyri and the superior parietal cortex (Gevins et al., 1996). The verbal activity was generally smaller than the spatial activations for the early P200 activity and the later left frontal activity at 300-900 ms (Gevins et al., 1996). Note that they did not

examine activity in the ventral extrastriate visual areas, as these regions were beyond the limits of their finite element modeling (see also Le & Gevins, 1993; Gevins et al., 1994). The components of working memory activity identified indicate several stages of information processing. Gevins et al. (1996) propose that the earlier frontal activity is involved in the early acquisition and evaluation of information in working memory and that it reciprocally interacts with the later parietal activation in the process of sustaining attention to the information retained in working memory. In particular, the left frontal activity at 450 ms is involved in sustained attention for sequential information, which is important for tracking the sequence of stimuli presented in their study. Also, the later parietal activity may be involved in the retention of amodal stimulus information in memory and the maintenance of attention for this stimulus information.

Delayed match to sample studies further illustrate the retention of information in working memory, with delays between sample and match stimuli in the order of several seconds (longer than sensory memory alone). These reports identify a posterior P3 for the sample stimuli and sustained frontal and parietal activity late in the delay interval (e.g., Ruchin, Johnson, Canoune & Ritter, 1990; Ruchin, Johnson, Grafman, Canoune & Ritter, 1992; Ruchin, Canoune, Johnson & Ritter, 1995; cf. Rämä, Carlson, Kekoni & Hämäläinen, 1995; Geffen et al., 1997; Löw et al., 1999). More demanding working memory comparisons induce increased P3 latency and duration, with some overlap of this activity with greater posterior positive slow wave amplitude, and increased frontal and parietal slow wave amplitude. The negative frontal and positive parietal slow waves are differentiated from the early P3 by their onset latency and extended activation during the delay periods, with enhanced activity for greater working memory loads, while the P3 tends to indicate initial stimulus evaluation activity (Ruchin et al., 1990). In addition, Geffen et al. (1997) demonstrate that the slow waves are maximal from 1 to

3 sec after sample onset, with enhanced amplitude when distracters are present during the delay interval. In essence, these differences suggest that P3 is associated with stimulus evaluation and early acquisition of information in working memory. The later frontal and parietal slow waves are related to retention of information in working memory, indicated by amplitude increases with more information retained and when the content of working memory might be displaced by distraction. The scalp topography of the negative frontal slow wave varies with different stimulus modalities and different encoding strategies. For example, Ruchin et al. (1990, 1995) report evidence of early modality specific activity, such as visual occipital negativity, followed by temporal and parietal components that are related to the storage of stimulus information, while a later frontal component indicates the retention and rehearsal of working memory content (see also Begleiter et al., 1993; Martin-Loeches, Gomez-Jarabo & Rubia, 1994; Gevins et al., 1995; Geffen et al., 1997; Löw et al., 1999). Moreover, a left lateralized frontal negativity for verbal information may indicate the level of activity in Baddeley's (1992) phonological loop, as it is related to phonological working memory load and neuropsychological tests of articulation rates (Ruchin et al., 1990, 1992, 1994; cf. Gevins et al., 1995).

Studies of human lesions of prefrontal cortex show impaired attention and working memory processes, including activity related to P3 and frontal negative potentials. Chao and Knight (1998) demonstrate that lesions of the human dorsolateral prefrontal cortex are related to excess thalamic and primary sensory cortex activity, resulting from decreased inhibitory control over these areas. This increases distraction and decreases resources available for working memory processing. Moreover, the prefrontal lesions were associated with deficits in a frontal negative potential, indicating impaired processing of relevant stimulus information, suggesting that prefrontal activity is normally involved in facilitating sustained attention for relevant sensory processing.

Similarly, Nielsen-Bohlman and Knight (1999) demonstrate that lesions of the human dorsolateral prefrontal cortex are related to decreased novelty P3a activity during a visual working memory task (see also Halgren & Marinkovic, 1995). They show that frontal lesions are related to smaller frontal P3a, but not parietal P3b activity, when subjects are required to evaluate whether a visual line drawing is a repeat of a previous stimulus (see also Daffner et al., 2000, 2003). This was the case when there were very short stimulus repetition delays (1.2 s) or longer delays (4-158 s), although the latter demonstrate greater deficits. The frontal lesions did not diminish posterior P3b activity, suggesting that the temporo-parietal junction (BA 39 & 40) maintains the activity generating the posterior P3b component, at least in the absence of the frontal region (Nielsen-Bohlman & Knight, 1999; see also Halgren & Marinkovic, 1995; Daffner et al., 2000, 2003). Furthermore, their study indicated a possible compensation for frontal impairment, consisting of greater N400 ERP activity during short delay periods, which suggests enhanced reliance on parietal and hippocampal interactions to maintain and evaluate stimuli during short delay matching processes (see also Halgren & Marinkovic, 1995). This is consistent with evidence that indicates important relationships between prefrontal and medial temporal regions (e.g., Goldman-Rakic & Friedman, 1991) and the possibility that activity in these networks is involved in novelty and associated episodic memory processing (e.g., Knight, 1996; Dolan & Fletcher, 1997; Daffner et al., 2000, 2003).

5.2.3 The Present Study

This study investigates updating of neutral words in working memory for PTSD patients. The task stimuli in this study were designed to promote the updating of relevant task information in working memory. As reviewed above, working memory processes may be elicited by non-target events that must be evaluated and retained for successful task performance (Rösler et al., 1985; Gevins et al., 1996). In this study,

working memory updating is differentiated from any response processing because there are no overt responses required for the non-target events (cf., Rösler et al., 1985; Gevins et al., 1996).

The cognitive tasks of this study are visual, verbal tasks that consist of the presentation of a series of red and blue words. Working memory is manipulated by two target detection criteria. In the first task, a *fixed target* was defined prior to task commencement. This task only requires a static working memory representation of a single target, which is compared with each new stimulus. In the second task, a *variable target* was defined by the repetition of any words in the attended color. Any attended word that is not a repeat of the previous attended word becomes a new target identity, so this task requires continual updating of a working memory representation of target attributes. Also, the attended words are randomly separated by up to three unattended words, so that all attended words must be retained in working memory for anywhere between 1.6 to 6.8 sec. Moreover, any intervening distraction from unattended words is likely to enhance the working memory activity (Geffen et al., 1997; see also Miller & Cohen, 2001). Comparison of the non-target ERPs for the variable and the fixed target task should reveal the extra processing required for updating the target identity in working memory.

All other aspects of these tasks are identical. Both tasks employ the same stimulus sequence and they both require selective attention to words of a given color and evaluation of each attended word against a working memory model of the target. Only the variable target task requires updating of the working memory target representation. It is possible that the fixed target task is amenable to automatic processing (e.g., Shiffrin & Schneider, 1977; Baddeley, 1992), in which case it would elicit even less working memory activity than the variable target task. Also, working memory updating for non-target words in this study is not associated with overt reaction

processes. In this study, we cannot preclude the possibility of covert response preparation (see Lee et al., 1999), but there is no response execution. If any response activity is involved, it may be response preparation followed by inhibition, which would be the same for both tasks. Note that no rewards or punishments were given for task performance, only speed and accuracy guided task training.

5.2.3.1 Stimulus Evaluation

As discussed in the previous chapter, all attended words are candidates for target detection. This requires evaluation of their attributes against those of the target representation. The previous chapter illustrates that these evaluation processes generate large scalp components at 250-600 ms over occipito-temporal, parietal and frontal regions. In this study, the scalp components for the attended non-target words of the fixed and variable target tasks are compared. It is expected that the variable target task will elicit not only stimulus evaluation, but also updating of the target representation in working memory.

5.2.3.2 Working Memory Updating

Stimulus evaluation processing will determine that a new word is not a target. As the previous chapter indicates, this process is complete within 300-600 ms. During this process, there is a working memory representation of both the current target and the new word. For the variable target task, whenever the new word does not match the target, it must replace the target in working memory and this controlled process may require greater energy, including deactivation of the network activity related to the previous target and enhanced network activity for the new target. This ongoing allocation of attention, consolidation and rehearsal for the new target is an additional processing task to all of those that are required in the fixed target task. The neural activity engaged in the executive control of this process could be expected to include

prefrontal regions, in collaboration with parietal areas, while the visual elements of the words could activate occipital and inferior temporal cortex. Thus, the updating of working memory for target attributes can be expected to elicit greater ERP activity over frontal, parietal and occipito-temporal regions. This activity can be expected largely after the time required for stimulus evaluation, so it may arise at 400-800 ms. As discussed above, similar work has previously identified that updating activity enhances the amplitude of positive potentials in this latency range (e.g., Rösler et al., 1985).

5.2.3.3 Dysfunction of Working Memory in PTSD

There is now a considerable literature on neuropsychology studies of PTSD, which have documented deficits in executive functions (Everly & Horton, 1989; Gil et al., 1990; Uddo et al., 1993; Yehuda et al., 1995; Anagnostaras et al., 1999; Vasterling et al., 2002). Initial investigation of verbal memory in PTSD demonstrated deficits in short-term retention and recall (Everly & Horton, 1989). Further investigation confirmed deficits in verbal memory and verbal fluency in PTSD patients (Gil et al., 1990; Sutker, Winstead, Galina & Allain, 1991; Bremner et al., 1993; although one study did not confirm some of these findings, see Yehuda et al., 1995). Several studies of auditory verbal learning and memory in PTSD indicate some impairment of information acquisition (Uddo et al., 1993) and susceptibility to interference of memory consolidation (Uddo et al., 1993; Yehuda et al., 1995). These findings imply defective or limited capacity to integrate information into verbal working memory and the associated consolidation of this information into episodic and semantic memory. Some findings also indicate deficits in executive processes, such as verbal fluency (Gil et al., 1990; cf. Yehuda et al., 1995), which suggest a general impairment of executive control of working memory content.

ERP studies can provide the temporal resolution and cognitive specificity for closer examination of attention and working memory processes. Several ERP studies

indicate neutral stimulus processing deficits in PTSD, which are the likely component processes involved in the deficits identified by neuropsychology studies. The impaired processing in PTSD has been indicated by delayed N2 and diminished P3 ERPs for rare target or distracter stimuli (see McFarlane et al., 1993; Charles et al., 1995; Metzger et al., 1997). The delayed N2 suggests abnormality of stimulus discrimination, while the diminished target P3 indicates deficits in contextual evaluation and maintenance of working memory representations for relevant stimulus attributes. The previous chapter investigated stimulus evaluation processes in PTSD and found evidence of deficits for visual stimuli. This chapter investigates the latter stages of working memory maintenance, which extends a recent study of auditory working memory in PTSD (Galletly et al., 2001). That study required detection of repeated tones, where successful performance required continual updating of the target identity after each non-target tone. The findings indicated that non-target tones elicit positive potentials that resemble the conventional target P3 (see also Clark et al., 1998). Furthermore, the study not only replicated previous findings of delayed N2 and diminished P3 in PTSD patients, but also demonstrated a deficit in non-target processing, which suggested impairment in the capacity for updating information in working memory. This finding is encouraging; it suggests a deficit in updating stimulus information in short-term sensory or working memory stores. However, the stimulus sequence in that study did not require extended retention and rehearsal of stimulus information, only continual updating of relevant target attributes, which may have facilitated sensory memory strategies. In this study, the visual stimulus sequence requires both continual updating and a variable degree of maintenance and rehearsal, with some degree of distraction from unattended stimuli. This more demanding task was designed to engage working memory stores and executive control processes, rather than sensory memory stores alone. Under these conditions, the deficit indicated in the previous work was expected

to be more conspicuous in the current study. Furthermore, this study provides a control condition, the non-target stimuli of the fixed target task, which was not available in the previous work (Galletly et al., 2001).

5.2.3.4 Hypotheses

The variable target task of this study requires both evaluation of attended words for target identity and updating of the target identity in working memory. Evaluation and working memory updating for attended words was expected to manifest in ERPs between 200-800 ms. The working memory updating activity in normal subjects was expected over frontal and parietal regions, with associated sensory activity over the occipital and posterior temporal regions. It was expected that measures of early sensory processing would be equivalent in PTSD patients and controls, consistent with previous findings (e.g. McFarlane et al., 1993; Charles et al., 1995; Metzger et al., 1997; Galletly et al., 2001). As an aside here, it should be noted that specific tasks and analyses can be employed to determine early sensory abnormalities in PTSD (e.g., Neylan et al., 1999), so this hypothesis is a reflection of experimental sensitivity, rather than knowledge about functional integrity in PTSD. In any case, it was expected that PTSD patients would demonstrate diminished working memory updating components in this study. If this activity is particularly related to executive functions of working memory, it can be expected that the frontal and parietal working memory activity will be most impaired. As discussed above, this hypothesis is based on previous findings of diminished target P3 ERPs in PTSD (McFarlane et al., 1993; Charles et al., 1995; Metzger et al., 1997; Galletly et al., 2001). Although this previous work employed auditory stimuli, the amplitude of the P3 has been shown to be invariant with stimulus modality; hence, these findings should generalize to the visual processing of this study. In contrast with these previous studies, the current study is a more specific investigation of working memory

updating, without the response execution confounds of the conventional target P3 (see also Galletly et al., 2001).

5.3 METHOD

See the general method chapter for details. This chapter examines working memory updating by comparison of the attended non-target words of the fixed and the variable target tasks. The previous chapter demonstrated the enhanced processing of attended non-target words in the fixed target task. This chapter investigates the additional process of not only evaluation of the attended word, but also the use of the attended non-target to update a working memory representation for the target identity. This was required for the variable target task, but it was not required for the fixed target task.

5.4 RESULTS

5.4.1 Task Performance

Patients were both slower to detect targets and detected fewer targets than controls, especially for the variable target task. This latter finding suggests that PTSD patients have difficulty with the greater demands on working memory for the variable target task. See the task performance chapter for further details.

5.4.2 ERP Signal-to-Noise Ratio

The number of EEG trials contributing to averaged ERPs for each condition and each group are summarized in Table 5-1. All subjects were presented with equal numbers of stimuli, but there were more EEG trials in the averaged ERPs for controls than PTSD patients and also for the fixed than the variable target task stimuli (group, $F[1,18] = 5.12$, $p<.05$; task, $F[1,18] = 40.29$, $p<.001$). Moreover, there was a greater

difference in the trials composing the fixed vs. variable target task ERPs for controls than PTSD patients (group x task, $F[1,18] = 5.02$, $p<.05$). There were fewer attended commons presented in the variable target task than the fixed target task, so the task differences are expected. The group differences are solely due to artifact reduction procedures. It is common for patient groups to generate more artifacts in ERP experiments than controls. Nevertheless, across all subjects and conditions, no less than 60 trials were averaged to provide a sufficient signal-to-noise ratio for endogenous ERP components arising near or after 80-100 ms (see Table 5-1).

Table 5-1. EEG trials in ERPs for working memory updating conditions.

Attended Commons	**Control** [a]				**PTSD** [a]			
	M	SD	Min	Max	M	SD	Min	Max
Fixed Target Task	209.80	(41.97)	166	271	153.80	(62.35)	64	264
Variable Target Task	170.90	(34.30)	126	221	135.20	(42.42)	70	221

[a] n = 10.

5.4.3 Event-Related Potential Components

5.4.3.1 Group Means

The topographic layout of group mean ERP waveforms is given in Figure 5-1 and Figure 5-2; the superimposed waveforms for each working memory condition and their difference are given in Figure 5-3. The waveforms demonstrate a consistent ERP component structure in response to all common stimuli, for both groups (see Figure 5-3). The components comprise:

- fronto-central N80 and posterior temporal P90 (see Figure 5-4 & Figure 5-7; note the occipital negativity develops further and peaks at 150 ms),
- occipital N150 and frontal P150 (see Figure 5-4 & Figure 5-8),
- occipital P250 and posterior temporal N300 (see Figure 5-5, Figure 5-9 & Figure 5-10),

- frontal P400 and parietal P550 (see Figure 5-6, Figure 5-11 & Figure 5-12),

Summary statistics for these components are given in Table 5-2 and the inferential analyses are described below (see Table 5-3), with the mean differences for significant effects.

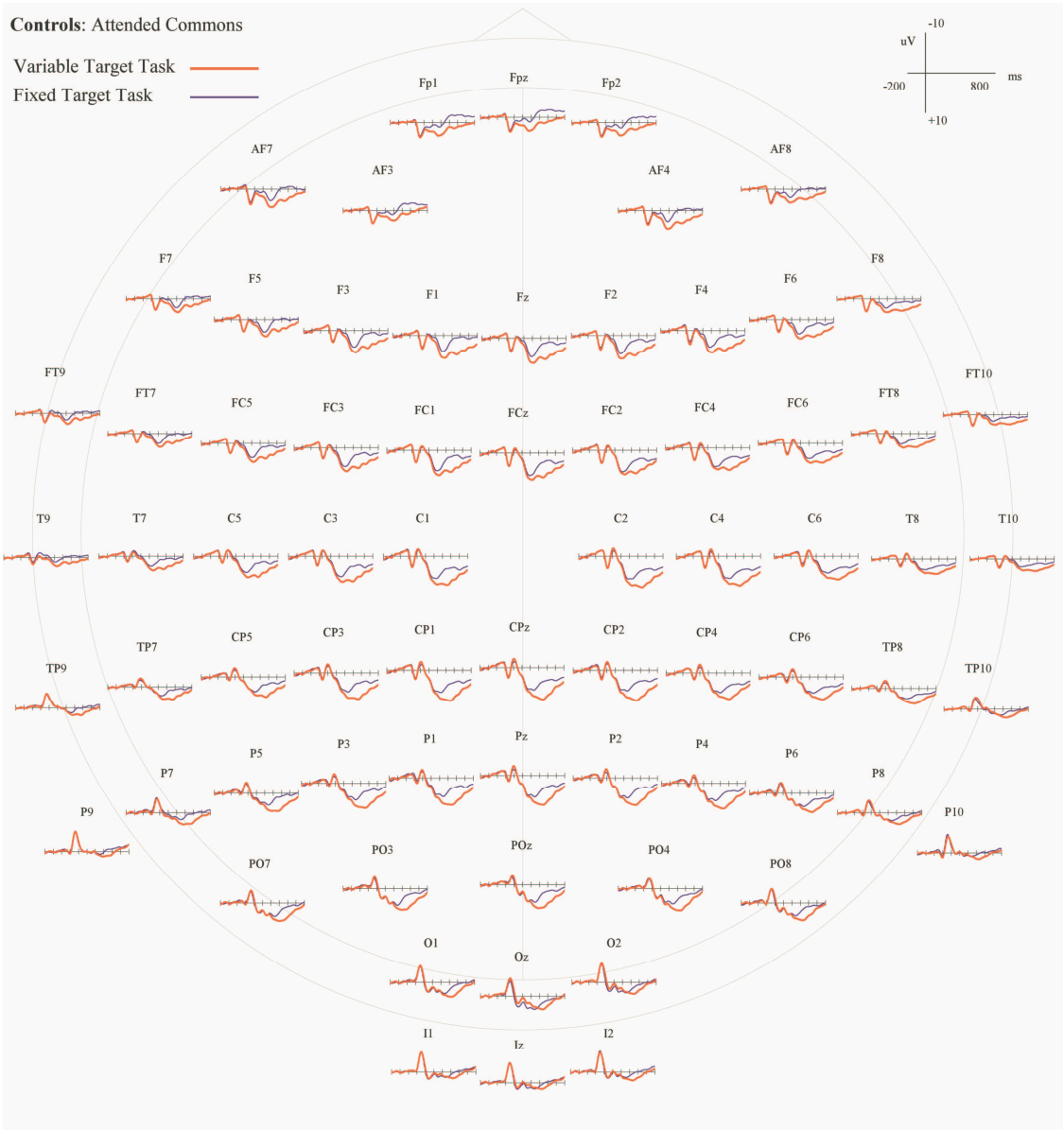

Figure 5-1. ERPs for attended common words in controls (n=10) at 70 scalp sites (-200 to 800 ms, 100 ms intervals). The variable target task elicits larger positive potentials than the fixed target task over occipital, parietal and frontal regions.

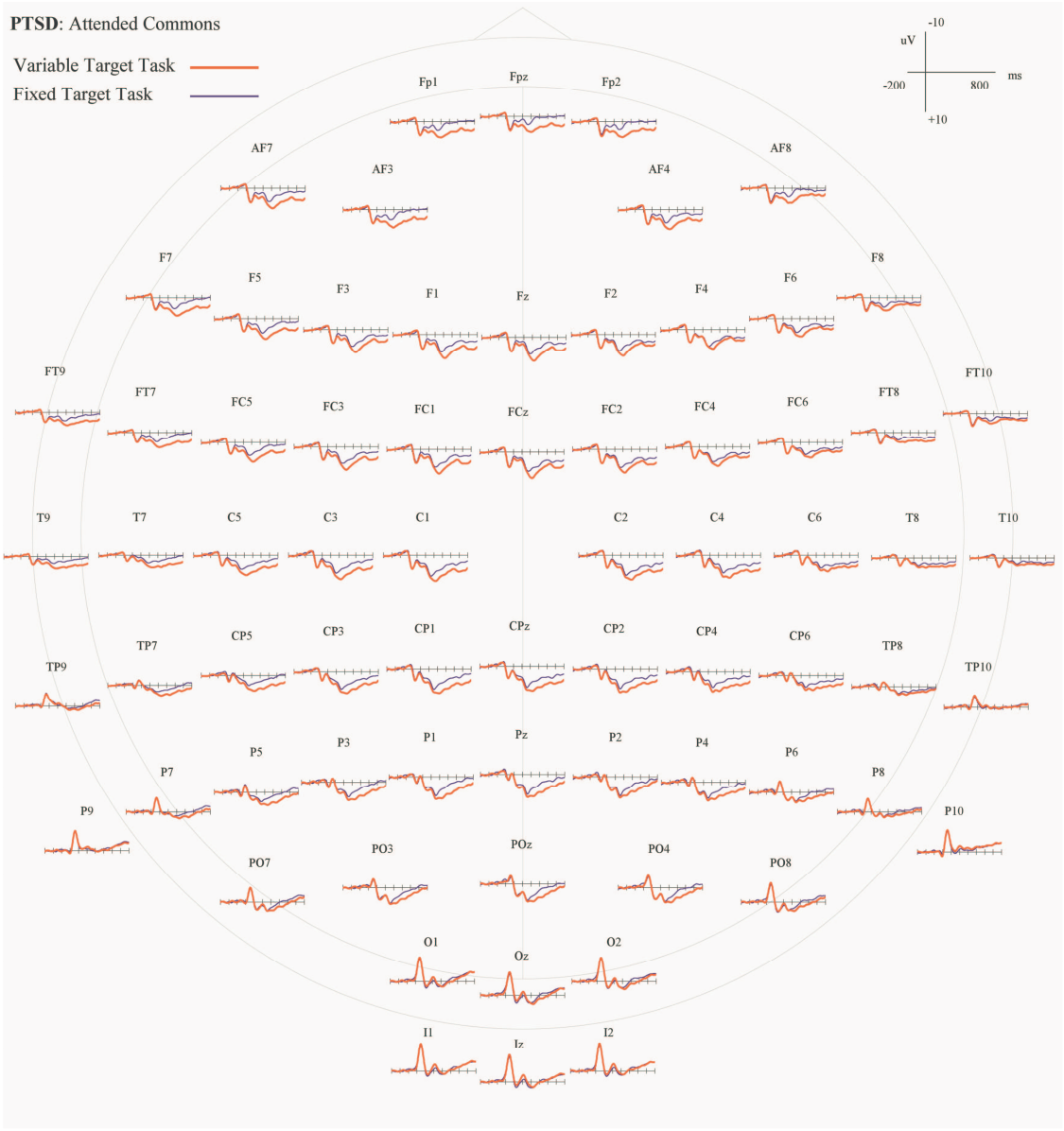

Figure 5-2. ERPs for attended common words in PTSD patients (n=10) at 70 scalp sites (-200 to 800 ms, 100 ms intervals). In comparison with controls, there is less difference between the fixed and variable target tasks in the amplitude of the positive potentials over occipital, parietal and frontal regions.

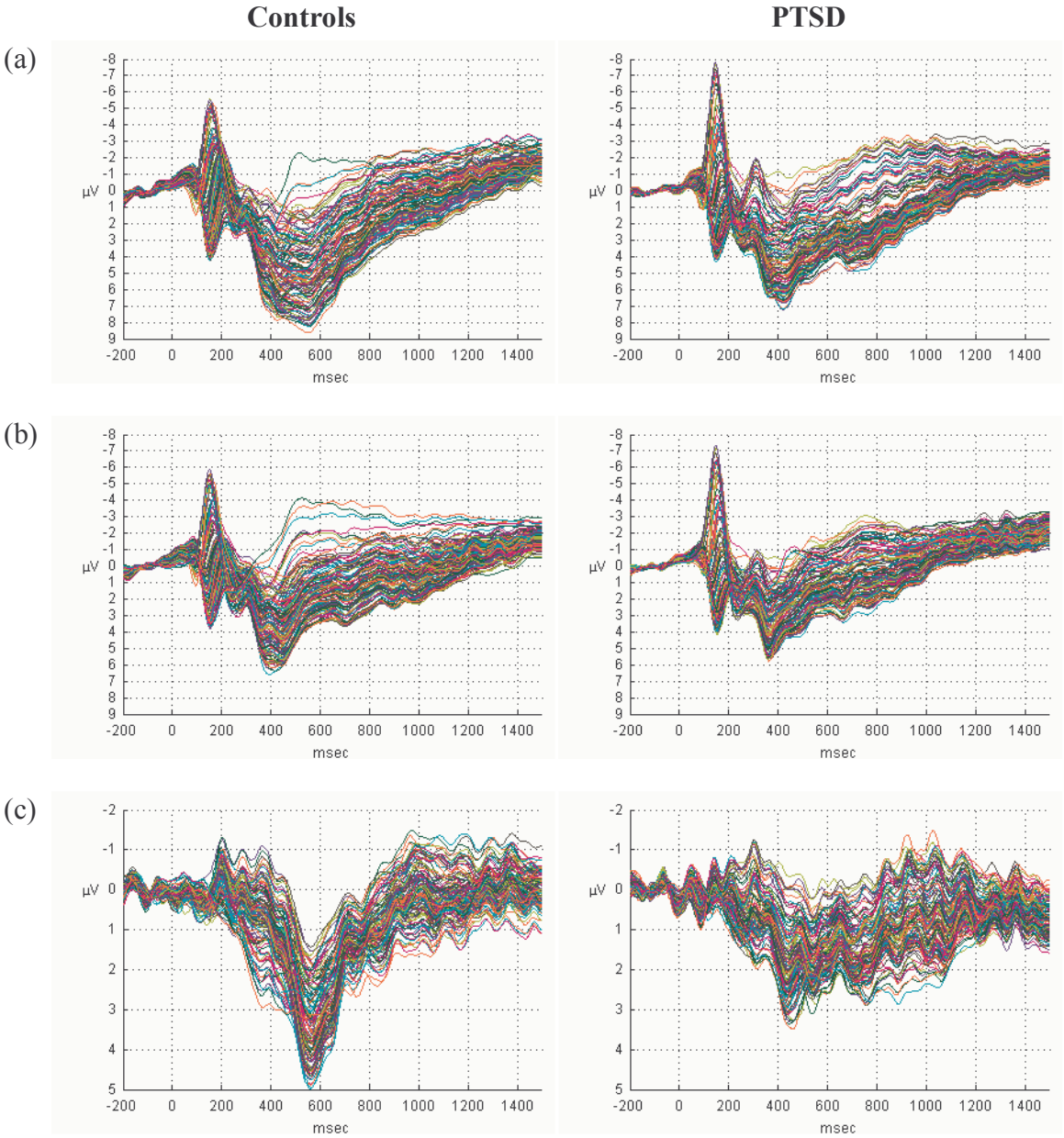

Figure 5-3. ERP waveforms at 124 scalp sites for attended common words in controls (n=10) and PTSD patients (n=10): (a) variable target task, (b) fixed target task, (c) variable - fixed.

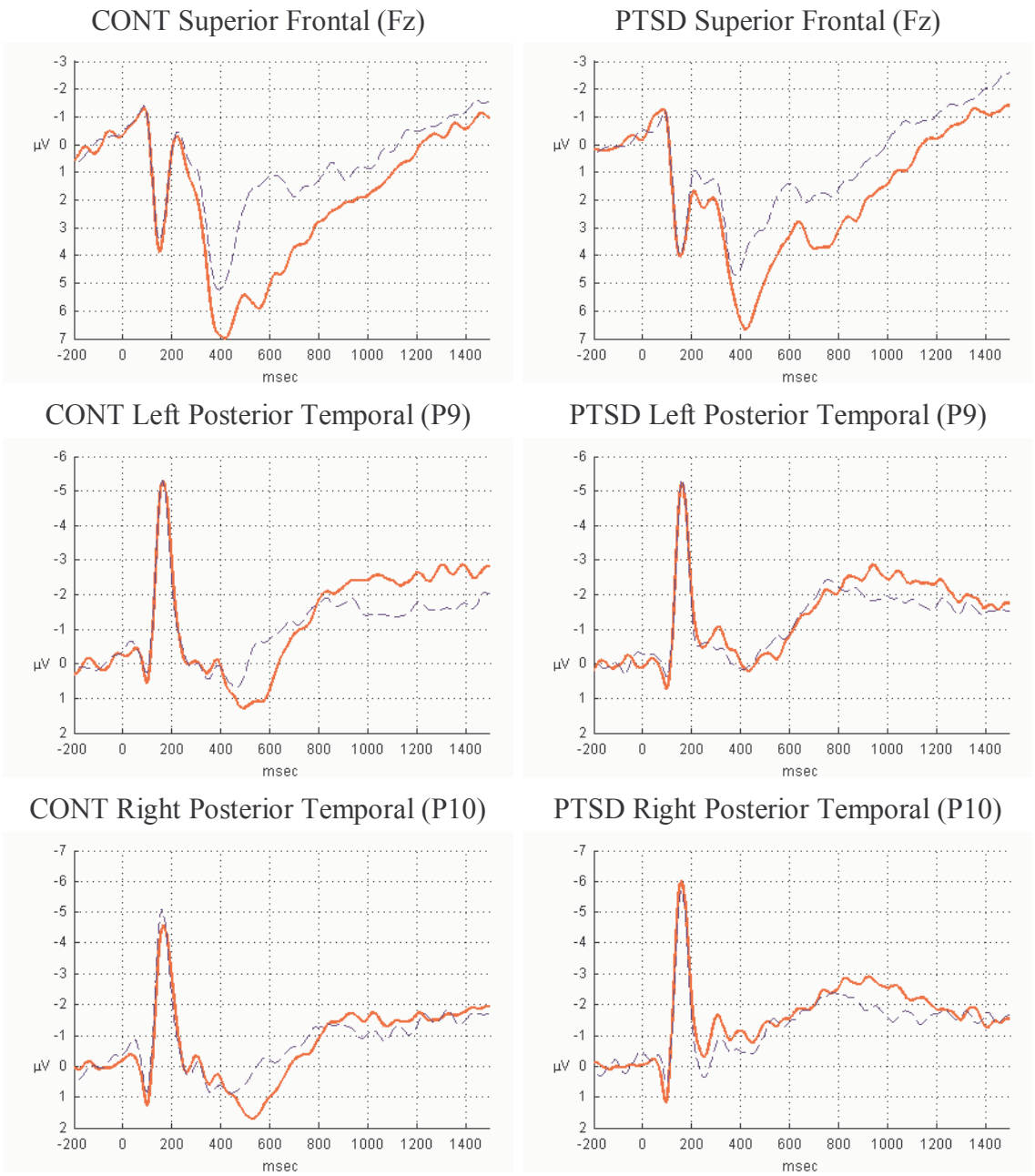

Figure 5-4. ERPs for controls (n = 10) and PTSD patients (n = 10) at frontal and temporal sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the early components: a small temporal P90 followed by a larger N150 and a small frontal N80 followed by a larger P150. Also, the frontal P400 is apparent (discussed further below) and the P550 appears in the posterior temporal regions for controls, possibly indicating extrastriate involvement in working memory updating (although the P550 peaks at parietal regions, see below).

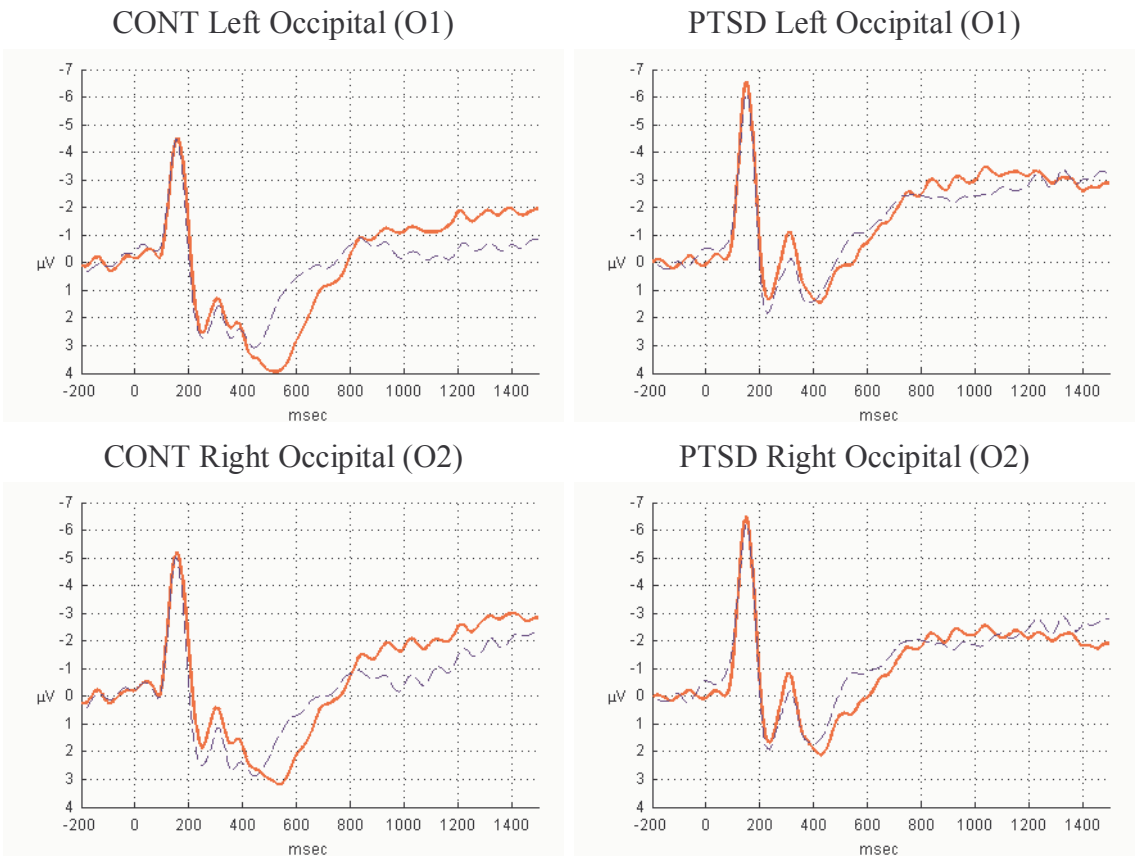

Figure 5-5. ERPs for controls (n = 10) and PTSD patients (n = 10) at occipital sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the larger N150 in PTSD patients and the following P250 and N300 components. Also note how the P550 is apparent in the occipital regions for controls, possibly indicating primary visual cortex involvement in working memory updating (although the P550 peaks at parietal regions, see below).

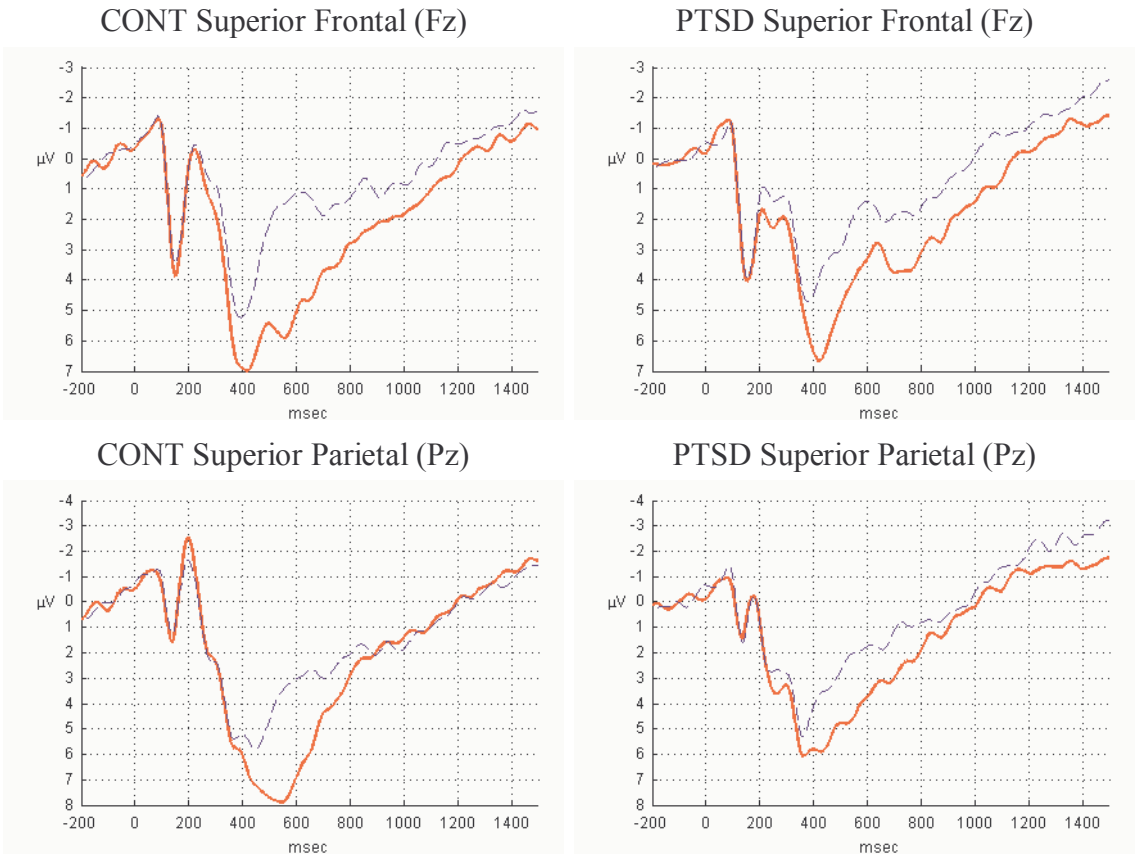

Figure 5-6. ERPs for controls (n = 10) and PTSD patients (n = 10) at frontal and parietal sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the large frontal P400 and the larger parietal P550, which is greater in controls than patients. Also note that these components most clearly differentiate the working memory conditions, indicating the updating and retention of new information in working memory. The earlier frontal potential may indicate frontal executive engagement and evaluation of non-target words, followed by parietal activation of storage processes and finally the frontal extended activity may indicate initial retention and the beginning of a frontal negative potential often reported in delayed match to sample studies.

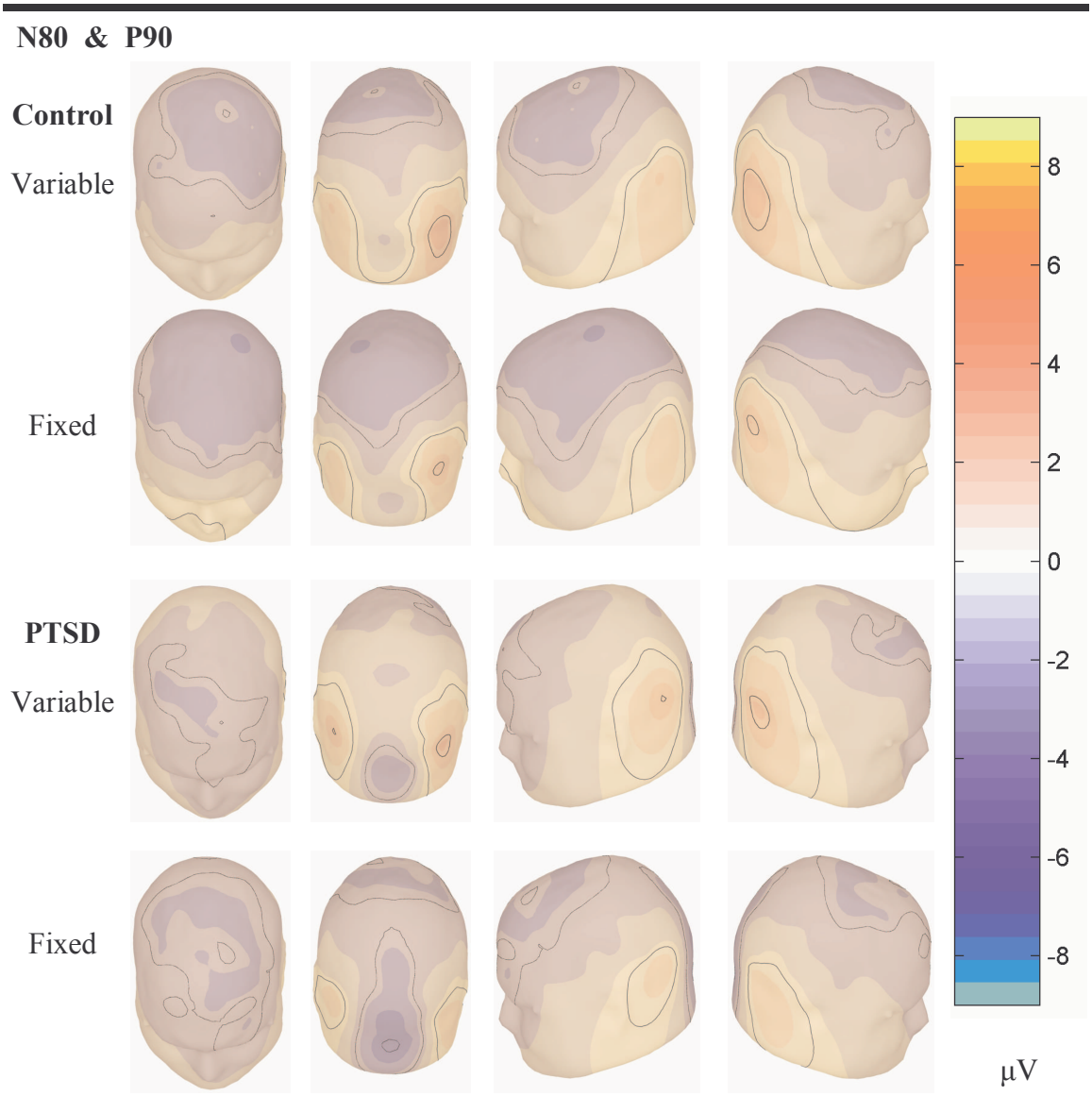

Figure 5-7. N80 & P90 ERP topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 95 ms, contours at 1 µV intervals.

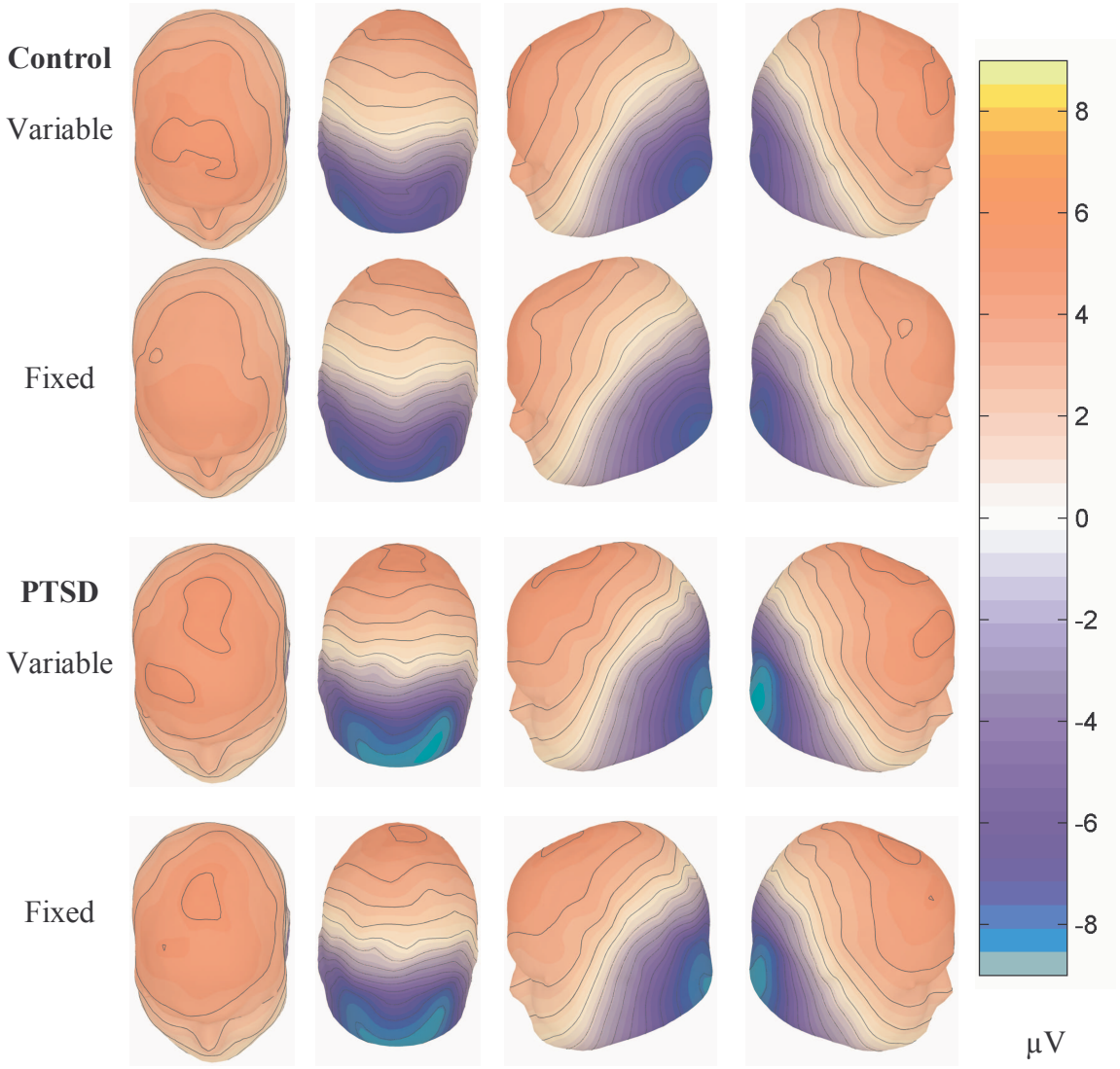

Figure 5-8. P150 & N150 ERP topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 150 ms, contours at 1 µV intervals.

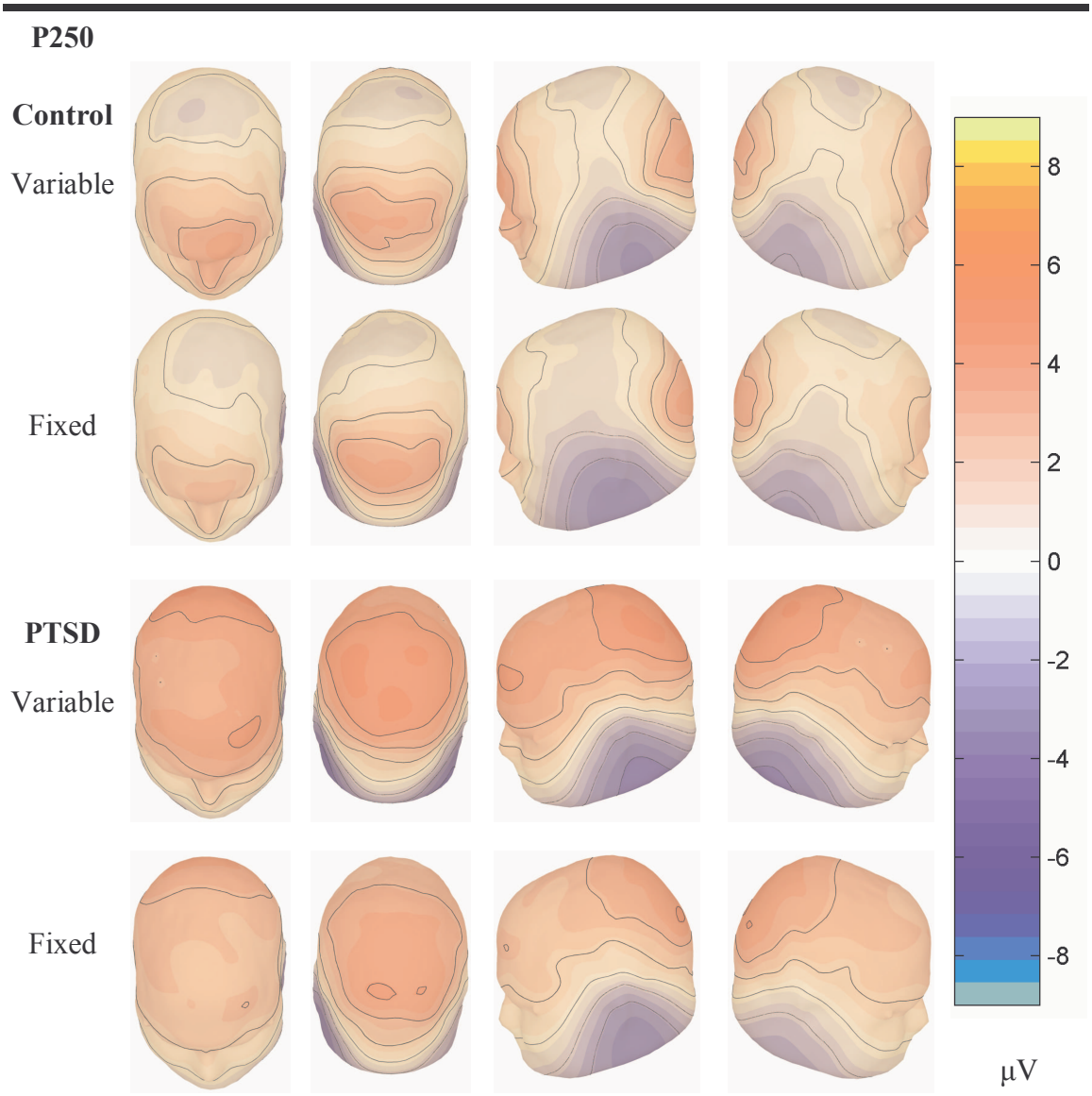

Figure 5-9. P250 ERP topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 250 ms, contours at 1 µV intervals.

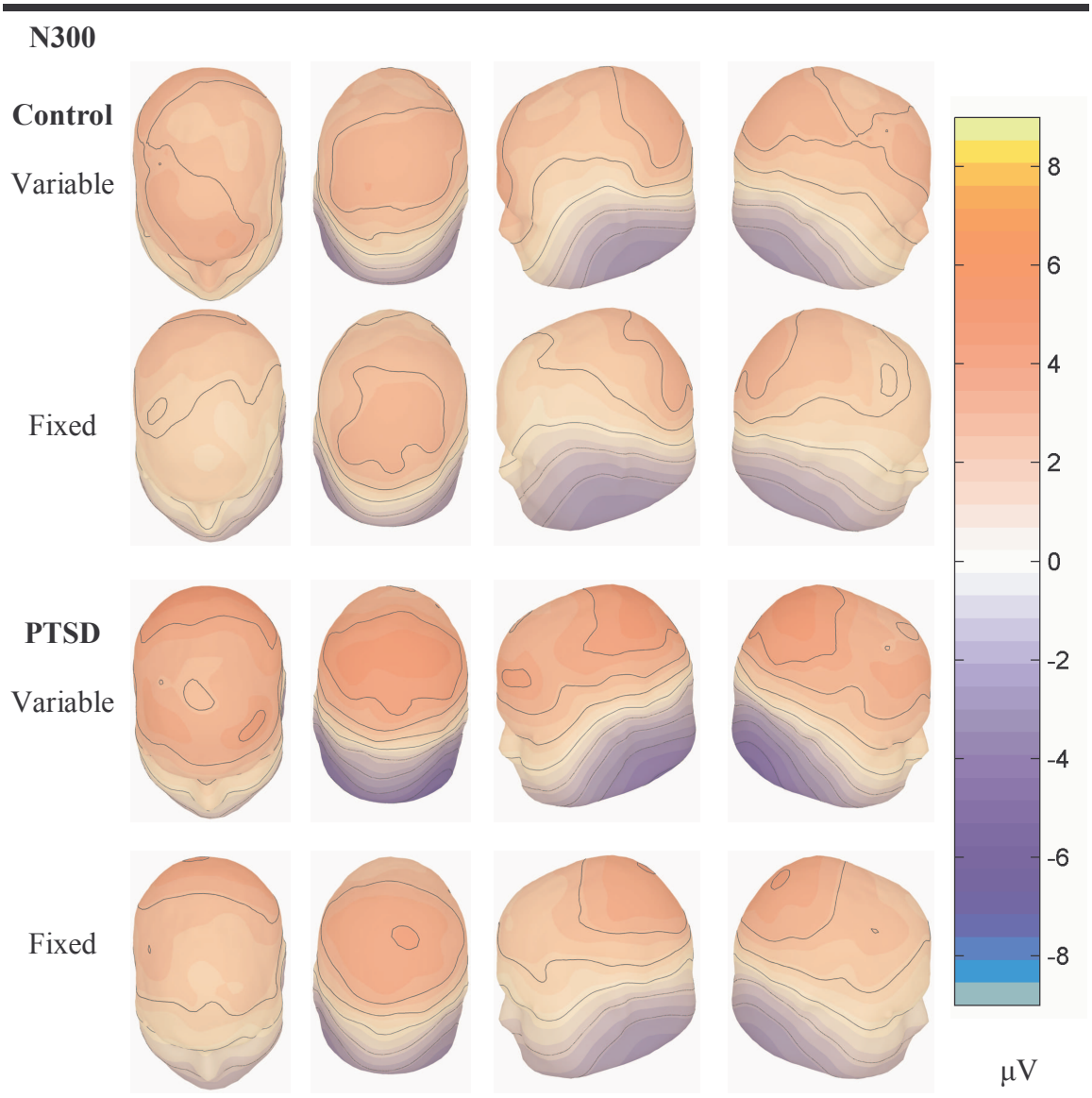

Figure 5-10. N300 ERP topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 300 ms, contours at 1 μV intervals.

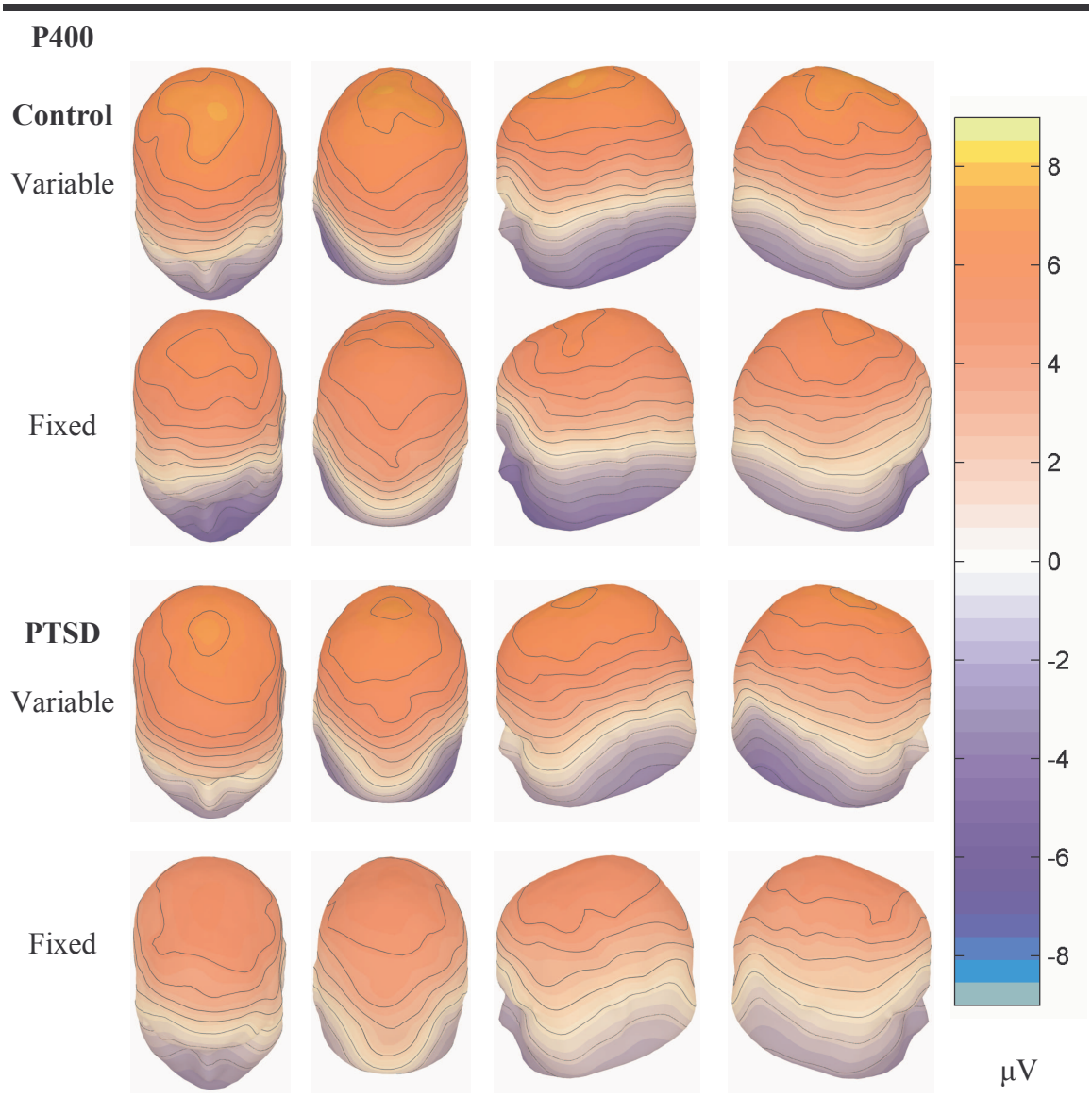

Figure 5-11. P400 ERP topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 410 ms, contours at 1 μV intervals.

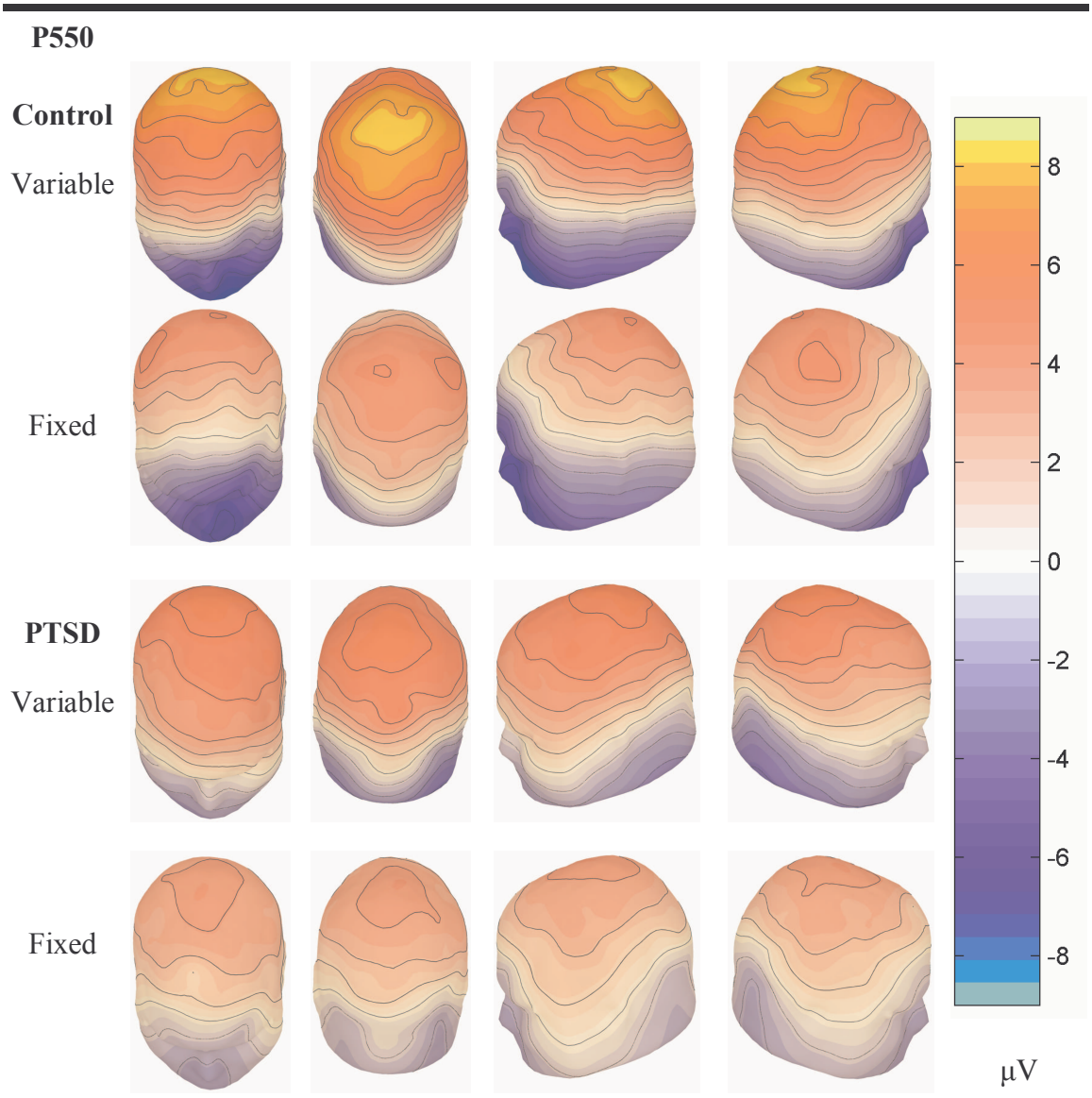

Figure 5-12. P550 ERP topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 530 ms, contours at 1 μV intervals.

Table 5-2. ERP Summary Statistics for Attended Common Words in Variable and Fixed Target Tasks [a] (continued overleaf).

			Amplitude (μV)		Latency (ms)	
			CONT	PTSD	CONT	PTSD
N80	Left	V	-2.05 (1.04)	-1.46 (1.02)	90.00 (7.73)	83.00 (9.99)
SF		F	-1.67 (0.65)	-1.48 (0.89)	88.50 (5.92)	82.25 (7.95)
	Right	V	-1.91 (1.30)	-1.70 (1.03)	85.50 (5.75)	81.50 (8.27)
		F	-1.58 (0.65)	-1.34 (0.76)	84.00 (5.55)	79.75 (8.70)
P90	Left	V	1.10 (1.86)	1.54 (1.66)	92.75 (3.62)	93.75 (12.09)
PT		F	0.50 (1.45)	1.07 (1.59)	89.75 (4.32)	92.75 (9.82)
	Right	V	1.91 (1.17)	1.92 (1.98)	93.75 (9.66)	93.50 (9.59)
		F	1.11 (1.36)	0.86 (2.12)	94.25 (5.66)	93.75 (10.36)
P150	Left	V	4.94 (2.37)	5.27 (3.17)	148.50 (14.10)	156.00 (16.88)
SPF		F	4.08 (2.03)	4.83 (2.58)	151.75 (13.80)	155.75 (13.02)
	Right	V	5.06 (2.61)	5.37 (3.28)	149.25 (15.05)	157.50 (15.50)
		F	4.46 (2.52)	4.90 (2.83)	152.00 (14.57)	157.50 (13.02)
N150	Left	V	-6.95 (4.37)	-8.55 (4.19)	157.75 (16.81)	150.75 (9.86)
OC		F	-6.42 (4.22)	-7.86 (4.21)	154.25 (14.63)	153.00 (9.63)
	Right	V	-7.10 (3.77)	-8.61 (3.28)	158.50 (15.51)	146.50 (9.59)
		F	-6.28 (3.83)	-7.90 (3.33)	156.00 (14.00)	149.25 (9.28)

[a] Values are mean (SD); V = variable target task, attended common words; F = fixed target task, attended common words; CONT, n = 10; PTSD, n = 10.

Table 5-2 (continued). ERP Summary Statistics for Attended Common Words in Variable and Fixed Target Tasks [a]

			Amplitude (μV)		Latency (ms)	
			CONT	PTSD	CONT	PTSD
P250	Left	V	3.95 (2.93)	5.05 (3.90)	252.25 (24.05)	242.75 (33.57)
OC		F	4.09 (2.30)	4.60 (3.74)	255.75 (24.44)	242.25 (30.08)
	Right	V	4.19 (2.29)	4.17 (3.50)	252.00 (24.43)	247.75 (29.07)
		F	3.64 (2.28)	4.23 (3.99)	253.25 (24.18)	244.00 (25.93)
N300	Left	V	-1.56 (2.10)	-2.25 (4.17)	301.75 (26.56)	303.00 (32.46)
PT		F	-1.25 (2.08)	-1.02 (3.17)	301.25 (26.80)	295.75 (21.41)
	Right	V	-1.28 (2.27)	-2.15 (3.25)	298.25 (21.18)	305.75 (16.16)
		F	-0.25 (1.85)	-1.37 (3.25)	305.75 (12.19)	303.25 (16.75)
P400	Left	V	9.20 (2.74)	8.02 (4.11)	417.50 (40.16)	417.00 (31.11)
SF		F	7.44 (4.11)	6.12 (3.29)	410.00 (34.52)	394.50 (38.49)
	Right	V	8.59 (2.98)	7.80 (4.02)	408.50 (33.48)	414.75 (31.17)
		F	7.39 (3.11)	6.00 (3.31)	407.25 (32.35)	382.50 (29.49)
P550	Left	V	9.77 (3.68)	5.98 (2.86)	527.75 (43.16)	537.75 (54.59)
SP		F	4.47 (2.12)	3.19 (2.32)	531.75 (64.32)	559.25 (51.83)
	Right	V	8.85 (3.06)	5.80 (3.20)	529.00 (46.36)	550.75 (54.86)
		F	4.83 (2.83)	3.05 (2.00)	515.75 (54.94)	552.75 (63.11)

[a] Values are mean (SD); V = variable target task, attended common words; F = fixed target task, attended common words; CONT, n = 10; PTSD, n = 10.

Table 5-3. Inferential Statistics for Working Memory ERP Components [a]

ERP		GP	WM	GPxWM	HS	GPxHS	WMxHS	GPxWMxHS
N80	Amp	0.85	1.53	0.19	0.15	1.00	0.45	0.74
SF	Lat	3.85	1.06	0.01	7.59*	1.12	0.07	0.07
P90	Amp	0.10	7.51*	0.01	1.39	0.88	4.08	1.02
PT	Lat	0.08	0.29	0.08	0.73	0.42	0.95	0.21
P150	Amp	0.16	5.05*	0.27	1.21	0.32	0.45	0.61
SPF	Lat	1.01	0.85	1.00	2.81	0.79	0.05	0.44
N150	Amp	0.84	6.92*	0.00	0.00	0.00	0.55	0.37
OC	Lat	1.63	0.04	4.86*	0.64	2.35	0.85	0.09
P250	Amp	0.15	0.63	0.00	4.43*	2.25	0.13	4.80*
OC	Lat	0.61	0.00	1.14	0.24	1.34	1.04	0.03
N300	Amp	0.27	19.66***	0.83	0.33	0.73	0.17	3.28
PT	Lat	0.00	0.07	2.42	0.29	0.19	0.79	0.05
P400	Amp	0.68	9.08**	0.12	0.69	0.07	0.77	0.39
SF	Lat	0.39	15.58***	8.17*	2.70	0.02	0.07	1.45
P550	Amp	5.24*	48.01***	3.12†	0.50	0.04	3.76	3.20
SP	Lat	1.65	0.06	0.33	0.13	0.87	8.14*	0.03

[a] Values are $F[1,18]$, GP = group, WM = working memory, HS = hemisphere.

* $p<.05$, ** $p<.01$, *** $p<.001$, *2-tailed*; † $p<.05$, †† $p<.01$, ††† $p<.001$, *1-tailed*.

5.4.3.2 N80 ERP

N80 peak amplitude was located between 40-110 ms, with the largest amplitude in the superior frontal region at 80-90 ms (see Figure 5-7 & Table 5-2). ANOVA indicated a significant difference between hemispheres in N80 latency (see Table 5-3). The N80 mean latency was later in the left than the right superior frontal region (M = 3.25 ms, SE = 1.18 ms, p<.05).

5.4.3.3 P90 ERP

P90 peak amplitude was located between 70-110 ms, with the largest amplitude in the posterior temporal region at 85-95 ms (see Figure 5-7 & Table 5-2). ANOVA indicated a significant working memory effect on P90 amplitude (see Table 5-3). There was a larger P90 peak for the variable target task than the fixed target task (M = 0.73 μV, SE = 0.27 μV, p<.05).

5.4.3.4 P150 ERP

P150 peak amplitude was located between 100-200 ms, with the largest amplitude in the superior prefrontal region at 145-160 ms (see Figure 5-8 & Table 5-2). ANOVA indicated a significant working memory effect on P150 amplitude (see Table 5-3). The mean P150 peak amplitude was larger for the variable target task than the fixed target task (M = 0.59 μV, SE = 0.26 μV, p<.05).

5.4.3.5 N150 ERP

N150 peak amplitude was located between 100-200 ms, with the largest amplitude in the occipital region at 145-160 ms (see Figure 5-8 & Table 5-2). ANOVA indicated a significant working memory effect on N150 amplitude (see Table 5-3). The mean N150 peak amplitude was larger (more negative) for the variable target task than the fixed target task (M = -0.69 μV, SE = 0.26 μV, p<.05). Also, ANOVA indicated a

significant interaction of group by working memory in N150 latency (see Table 5-3). However, relevant mean comparisons indicated no significant differences. That is, there were no working memory differences in mean N150 latency for controls (*M* = 3.00 ms, *SE* = 1.76 ms, *ns*) or PTSD patients (*M* = -2.50 ms, *SE* = 1.76 ms, *ns*). Similarly, there were no significant group differences in mean N150 latency for the fixed target task (*M* = 9.50 ms, *SE* = 5.69 ms, *ns*) or the variable target task (*M* = 4.00 ms, *SE* = 5.15 ms, *ns*).

5.4.3.6 P250 ERP

P250 peak amplitude was located between 200-300 ms, with the largest amplitude in the occipital region at 240-260 ms (see Figure 5-9 & Table 5-2). ANOVA indicated a significant interaction of group by working memory by hemisphere in P250 amplitude (see Table 5-3). This interaction was due to a hemisphere difference in patients for the variable target task; the mean P250 peak amplitude was larger over the left than the right occipital region in PTSD patients for the variable target task (*M* = 0.88 μV, *SE* = 0.33 μV, $p<.05$).

5.4.3.7 N300 ERP

N300 peak amplitude was located between 250-350 ms, with the largest amplitude in the posterior temporal region at 295-310 ms (see Figure 5-10 & Table 5-2). ANOVA indicated a significant working memory effect in N300 amplitude (see Table 5-3). The mean N300 peak amplitude was larger for the variable target task than the fixed target task over the bilateral posterior temporal regions (*M* = -0.84 μV, *SE* = 0.19 μV, $p<.001$).

5.4.3.8 P400 ERP

The P400 peak amplitude was located between 300-480 ms, with the largest amplitude in the superior frontal region at 380-420 ms (see Figure 5-11 & Table 5-2). ANOVA indicated a significant working memory effect in P400 amplitude (see Table

5-3). The mean P400 peak amplitude was larger for the variable target task than the fixed target task (M = 1.67 μV, SE = 0.55 μV, p<.01). Also, ANOVA indicated a significant interaction of group by working memory in P400 latency (see Table 5-3). The mean P400 latency was longer for the variable target task than the fixed target task for PTSD patients (M = 27.38 ms, SE = 5.69 ms, p<.001), but not for controls (M = 4.38 ms, SE = 5.69 ms, *ns*).

5.4.3.9 P550 ERP

The P550 peak amplitude was located between 450-650 ms, with the largest amplitude in the superior parietal region at 515-560 ms (see Figure 5-12 & Table 5-2). ANOVA indicated a significant interaction of group by working memory in P550 amplitude (see Table 5-3). The mean P550 peak amplitude was larger in the variable than the fixed target task (M = 3.72 μV, SE = 0.54 μV, p<.001). Also, the mean P550 peak amplitude was larger in controls than PTSD patients for the variable target task (M = 3.42 μV, SE = 1.40 μV, p<.05), but not for the fixed target task (M = 1.53 μV, SE = 0.98 μV, *ns*). Also, ANOVA indicated a significant interaction of working memory by hemisphere in P550 latency (see Table 5-3). However, relevant mean comparisons indicated no significant differences. That is, there was no working memory difference in either the left (M = -12.75 ms, SE = 13.52 ms, *ns*) or the right (M = 5.63 ms, SE = 15.48 ms, *ns*) superior parietal region and there was no hemisphere difference for either the fixed target task (M = 11.25 ms, SE = 6.93 ms, *ns*) or the variable target task (M = -7.13 ms, SE = 6.14 ms, *ns*).

5.4.3.10 Summary of ERP Findings

Significant differences were found in the following ERP components:

- a posterior temporal P90 was larger in the working memory updating condition at 90-95 ms,

- an occipital N150 and a superior prefrontal P150 were larger for the working memory updating condition at 145-160 ms,
- an occipital P250 was larger over the left than the right occipital region in PTSD patients for the working memory updating condition at 240-255 ms,
- a posterior temporal N300 was larger for the working memory updating condition at 295-305 ms,
- a superior frontal P400 was larger for the working memory updating condition at 380-420 ms and its latency was delayed for the working memory updating condition in PTSD patients, but not for controls, and
- a superior parietal P550 was larger for the working memory updating condition at 515-560 ms. Furthermore, the P550 peak amplitude was larger for controls than PTSD patients in the working memory updating condition.

5.4.4 ERP Difference Waves

The working memory difference waves demonstrate two periods of divergence (see Figure 5-3, Figure 5-13, Figure 5-14 & Figure 5-15). The first comprises small negative potentials over posterior regions, which peak at 100-350 ms (ND200/ND300, see Figure 5-14 & Figure 5-15). The second comprises large positive potentials over frontal and parietal regions, which peak at 400-600 ms (PD550, see Figure 5-14 & Figure 5-15). The summary statistics for these components are given in Table 5-4 and the inferential statistics are described below (see Table 5-5), with the mean differences for significant effects.

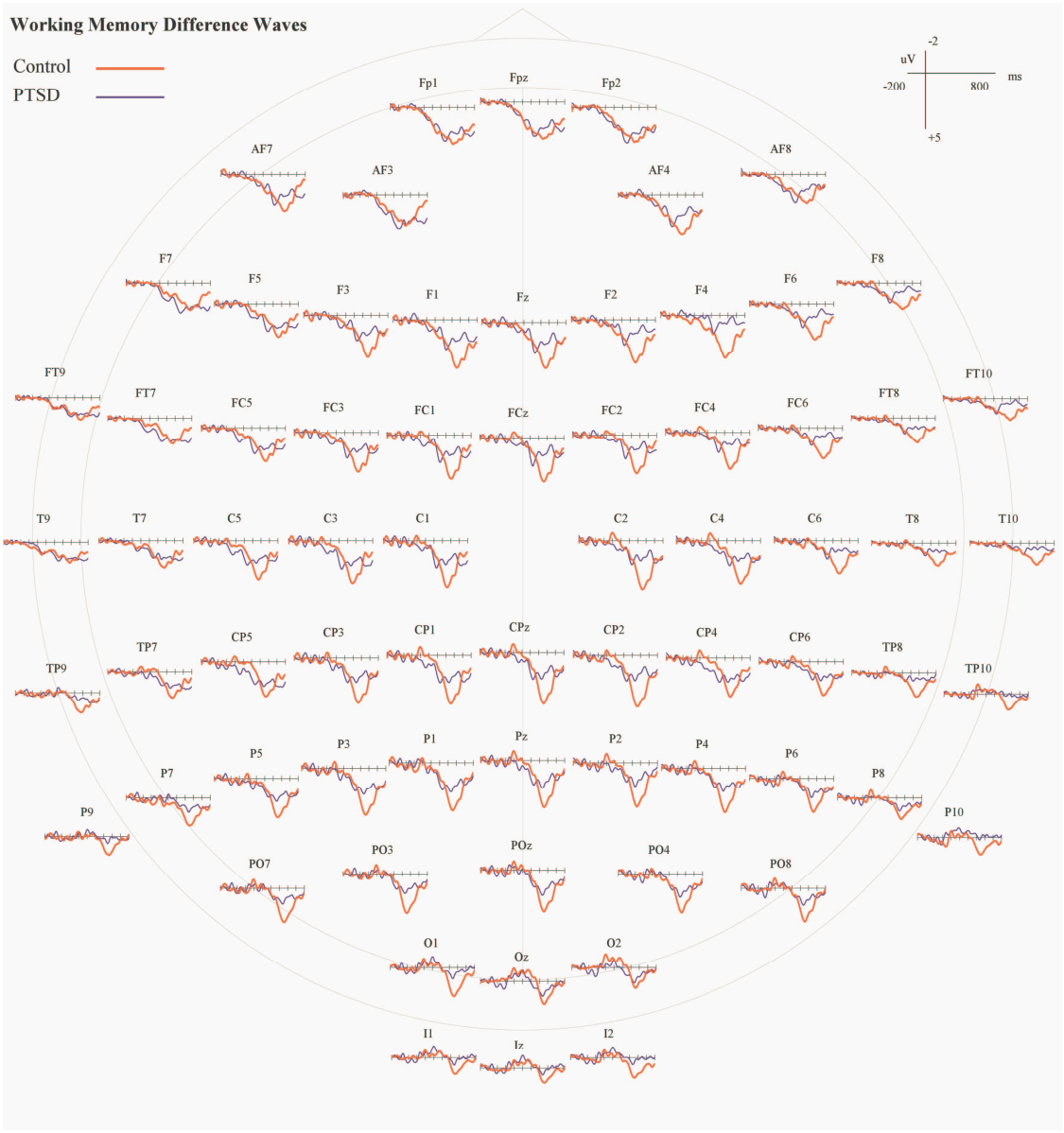

Figure 5-13. Working memory ERP difference waves in controls (n=10) and PTSD patients (n=10) at 70 scalp sites (-200 to 800 ms, 100 ms intervals). The controls demonstrate larger working memory updating activity over posterior and frontal regions at 500-700 ms.

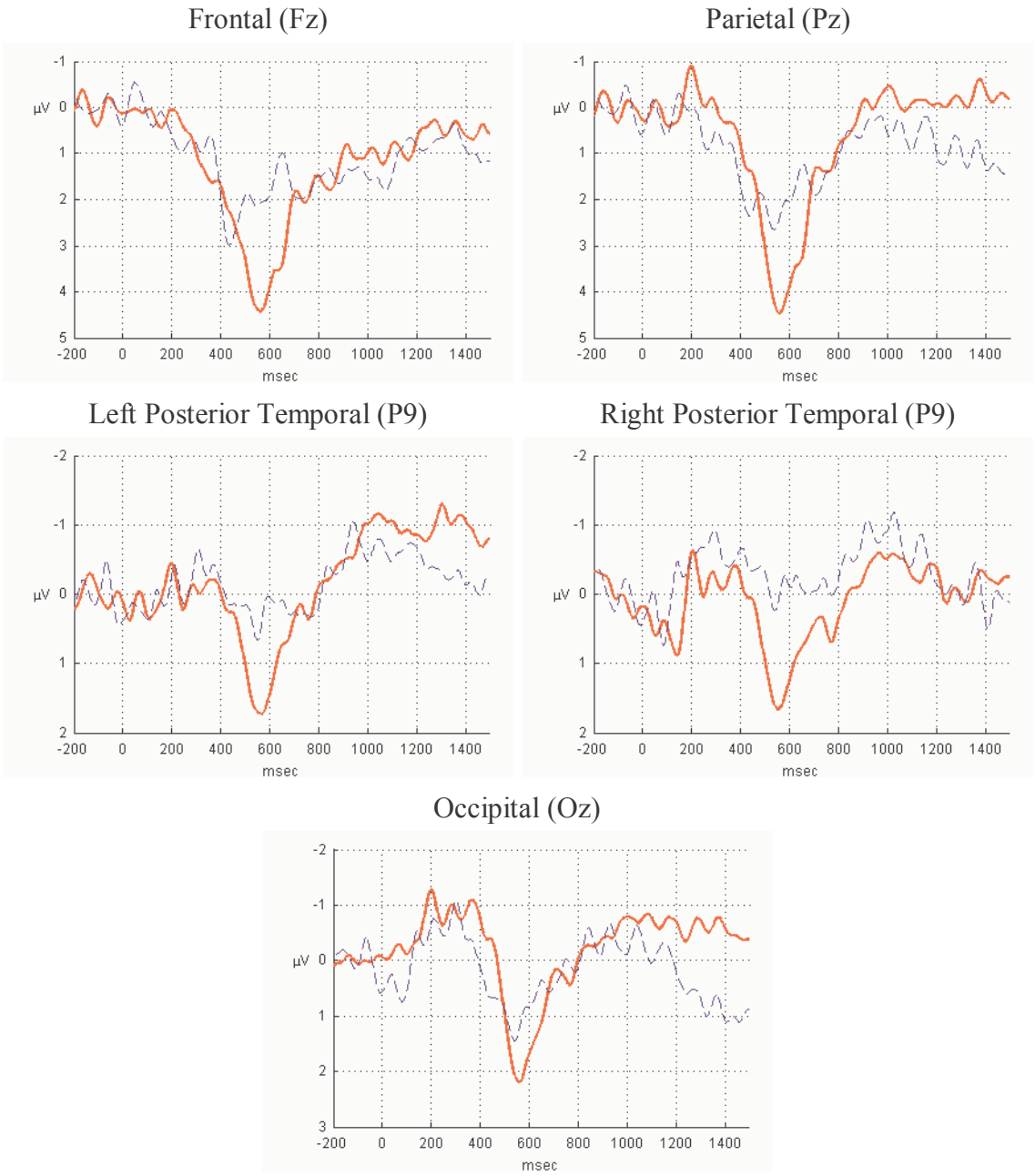

Figure 5-14. Working memory ERP difference waveforms for controls (n = 10; red, solid) and PTSD patients (n = 10; blue, dash). There is larger ND200/ND300 in controls than PTSD patients at the parietal and occipital regions. More importantly, there is larger PD550 in controls than patients at the frontal, parietal and posterior temporal regions.

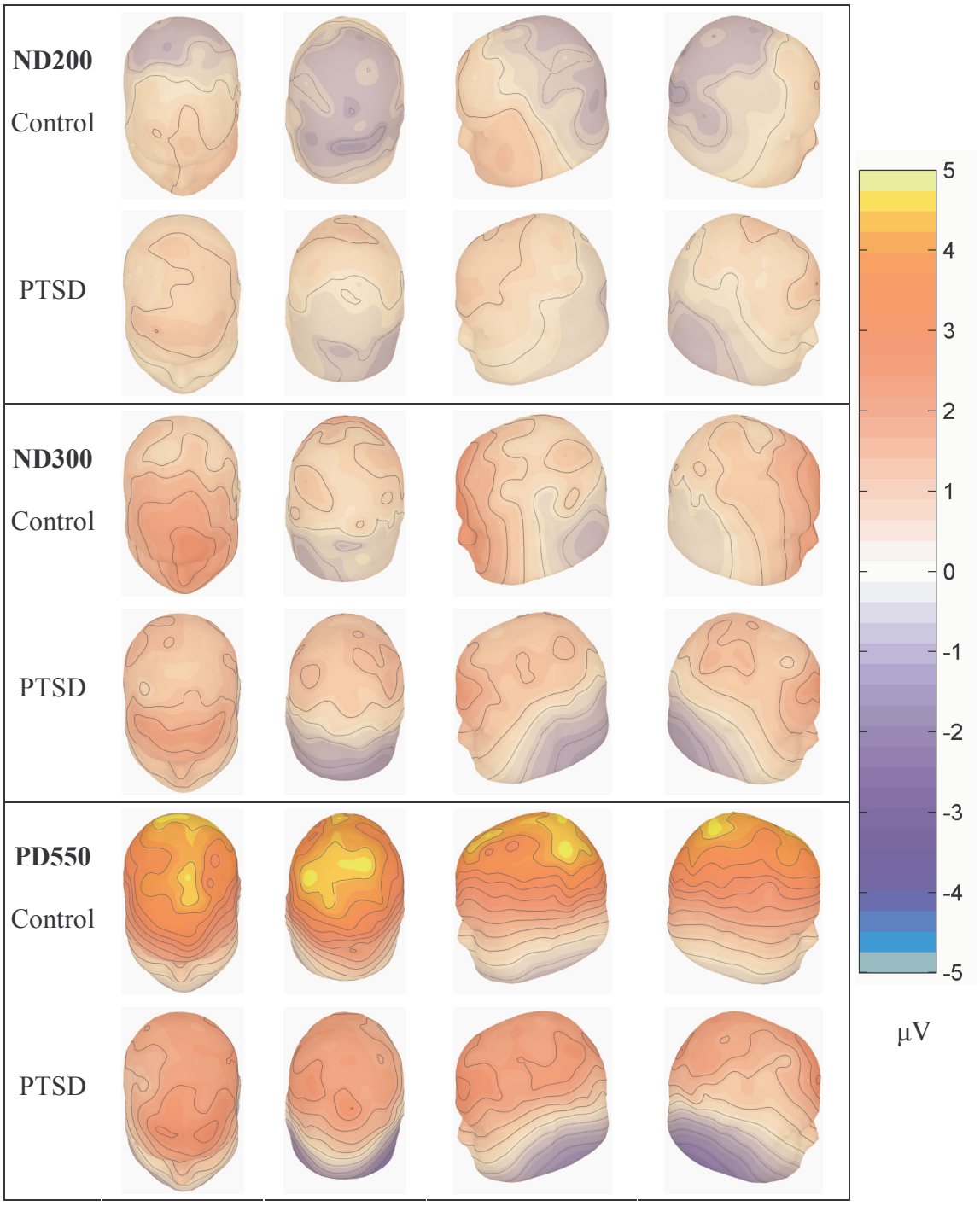

Figure 5-15. ND200, ND300 & PD550 ERP topography for controls (n = 10) and PTSD patients (n = 10) for the working memory difference wave (contours at 0.5 μV intervals). The ND200 is given at 200 ms, the ND300 is given at 330 ms and the PD550 is given at 575 ms. All maps are given on the same scale.

Table 5-4. Summary Statistics for Working Memory ERP Difference Components [a]

		Amplitude (μV)		Latency (ms)	
		CONT	PTSD	CONT	PTSD
ND200	Left	-1.16 (0.87)	-0.37 (1.47)	202.25 (36.22)	186.25 (18.46)
OC	Right	-1.83 (0.99)	-1.33 (1.46)	201.00 (12.54)	216.50 (25.03)
ND200	Left	-1.73 (0.93)	-0.81 (1.74)	204.25 (27.66)	198.00 (30.84)
IP	Right	-1.27 (1.03)	-1.00 (1.23)	204.25 (17.44)	202.00 (26.43)
ND300	Left	-1.14 (1.59)	-0.25 (1.81)	333.75 (55.32)	331.75 (34.72)
OC	Right	-2.20 (1.13)	-1.89 (1.23)	326.50 (50.10)	328.25 (49.06)
PD550	Left	6.11 (2.48)	4.37 (1.89)	592.00 (57.89)	492.50 (107.45)
SPF	Right	5.71 (2.32)	3.98 (1.69)	574.50 (48.96)	467.75 (80.36)
PD550	Left	6.35 (2.55)	4.26 (1.81)	571.25 (54.32)	555.00 (102.90)
SP	Right	5.34 (2.17)	4.28 (1.28)	583.50 (55.74)	555.50 (108.34)

[a] Values are mean (SD); CONT, n = 10; PTSD, n = 10.

Table 5-5. Inferential Statistics for Working Memory ERP Difference Components [a]

ERP		GP	HS	GPxHS
ND200	Amp	1.86	8.10*	0.27
OC	Lat	0.00	3.17	3.74
ND200	Amp	1.55	0.19	1.12
IP	Lat	0.18	0.12	0.12
ND300	Amp	1.08	18.92***	0.88
OC	Lat	0.00	0.16	0.02
PD550	Amp	3.71†	1.65	0.00
SPF	Lat	10.94**	2.07	0.06
PD550	Amp	3.41†	3.21†	3.43†
SP	Lat	0.36	0.54	0.46

[a] Values are F[1,18], GP = group, HS = hemisphere.

* p<.05, ** p<.01, *** p<.001, *2-tailed*; † p<.05, †† p<.01, ††† p<.001, *1-tailed.*

5.4.4.1 ND200 ERP

The ND200 peak was identified between 150-250 ms, with largest amplitude in the occipital region at 185-220 ms (see Table 5-4). ANOVA indicated a significant

hemisphere difference in ND200 amplitude (see Table 5-5). The mean ND200 amplitude was larger (more negative) over the right than the left occipital region (M = -0.81 μV, SE = 0.29 μV, p<.05).

The grand mean waveforms also indicate group differences in the parietal regions at approximately 200-300 ms (see Figure 5-13 & Figure 5-15). The ND200 was larger over the inferior than the superior parietal region (see Table 5-4). However, ANOVA indicated no significant differences (see Table 5-5).

5.4.4.2 ND300 ERP

The ND300 peak was identified between 250-450 ms, with largest amplitude in the occipital region at 325-335 ms (see Table 5-4). ANOVA indicated a significant hemisphere difference in ND300 amplitude (see Table 5-5). The ND300 was larger (more negative) over the right than the left occipital region (M = -1.35 μV, SE = 0.31 μV, p<.001).

5.4.4.3 PD550 ERP

The PD550 peak was identified between 300-700 ms, with largest amplitude at superior prefrontal and superior parietal regions between 465-595 ms (see Figure 5-15 & Table 5-4). Note the greater variability in peak latency for PTSD patients (cf. Neylan et al., 2003).

Superior prefrontal: ANOVA indicated a significant group difference in PD550 amplitude and latency (see Table 5-5). The mean PD550 peak amplitude was larger in controls than PTSD patients (M = 1.73 μV, SE = 0.90 μV, p<.05, *1-tailed*). Also, the mean PD550 peak latency was longer in controls than PTSD patients (M = 103.13 ms, SE = 31.18 ms, p<.01).

Superior parietal: ANOVA indicated a significant interaction of group and hemisphere in PD550 amplitude (see Table 5-5). The mean PD550 peak amplitude was

larger in controls than PTSD patients over the left superior parietal region (M = 2.01 μV, SE = 0.99 μV, p<.05), but not the right superior parietal region (M = 1.06 μV, SE = 0.80 μV, *ns*). Also, the mean PD550 peak amplitude was larger over the left than the right superior parietal region in controls (M = 1.02 μV, SE = 0.39 μV, p<.05), but not in PTSD patients (M = -0.02 μV, SE = 0.39 μV, *ns*).

5.4.4.4 Summary of ERP Difference Component Findings

At 465-595 ms, the PD550 peak amplitude was larger for controls than PTSD patients over the superior prefrontal region and the left superior parietal region. The duration was also longer in controls than PTSD patients over the superior prefrontal region.

5.4.5 Scalp Current Density Components

5.4.5.1 Group Means

The working memory condition waveforms are illustrated in Figure 5-16 and Figure 5-17. The time course of SCD components is clear in the superimposed waveforms for each condition and the difference waves in Figure 5-18. The following SCD components were identified and further analyzed:

- superior frontal N80 (see Figure 5-19 & Figure 5-20),
- posterior temporal P100 (see Figure 5-21 & Figure 5-22),
- parietal P150 and occipital N150 (see Figure 5-23 Figure 5-24),
- occipital P250 and frontal N250 (see Figure 5-25 & Figure 5-26),
- parietal P350 and P500 (see Figure 5-27, Figure 5-28 & Figure 5-29)

Summary statistics for these components are given in Table 5-6 and the inferential analyses are described below (see Table 5-7), with the mean differences for significant effects.

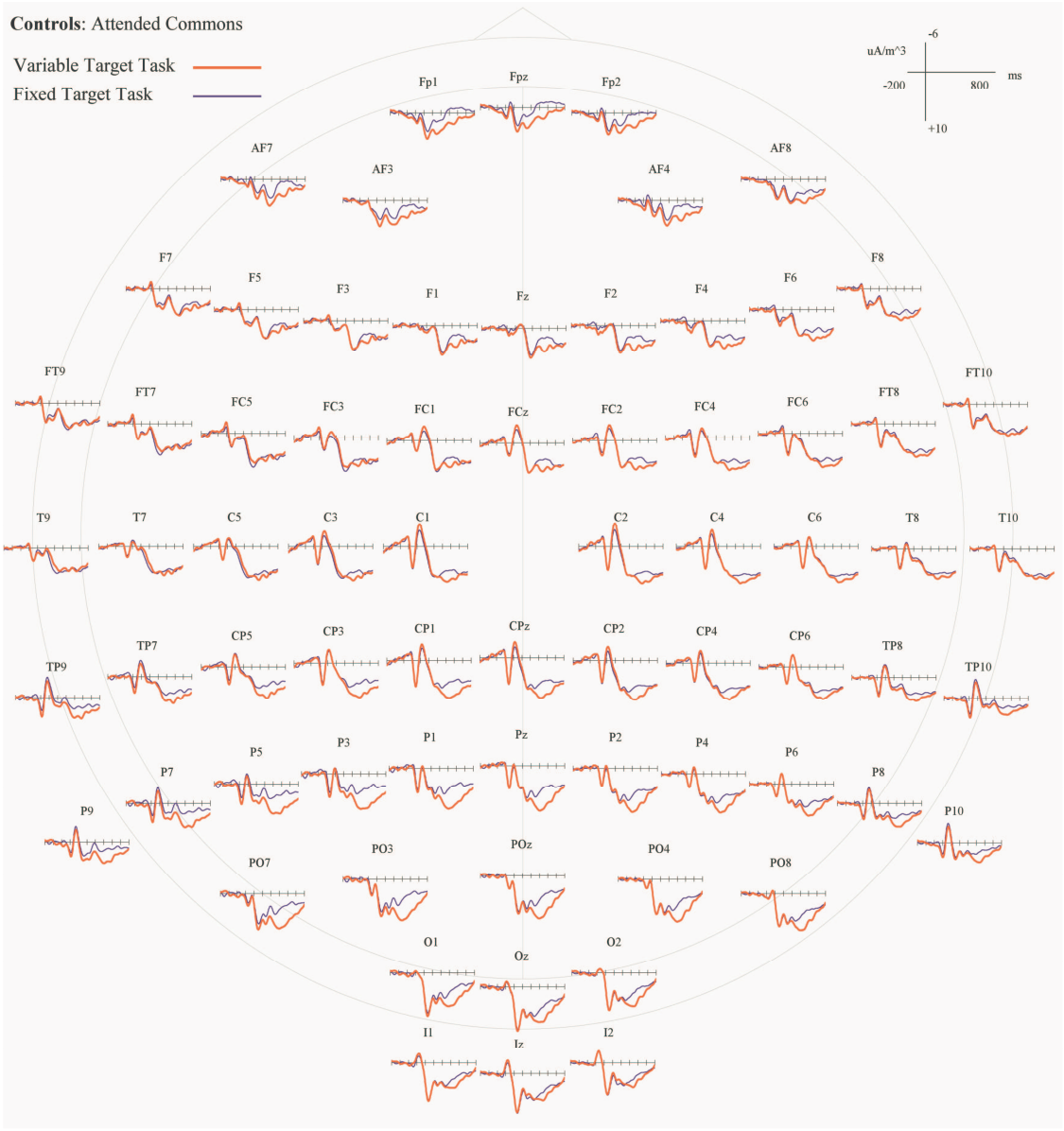

Figure 5-16. Event-related SCD in controls (n=10) at 70 scalp sites (-200 to 800 ms, 100 ms intervals). Attended non-target words in the variable target task elicit larger positive SCD over the posterior and prefrontal regions at 400-600 ms.

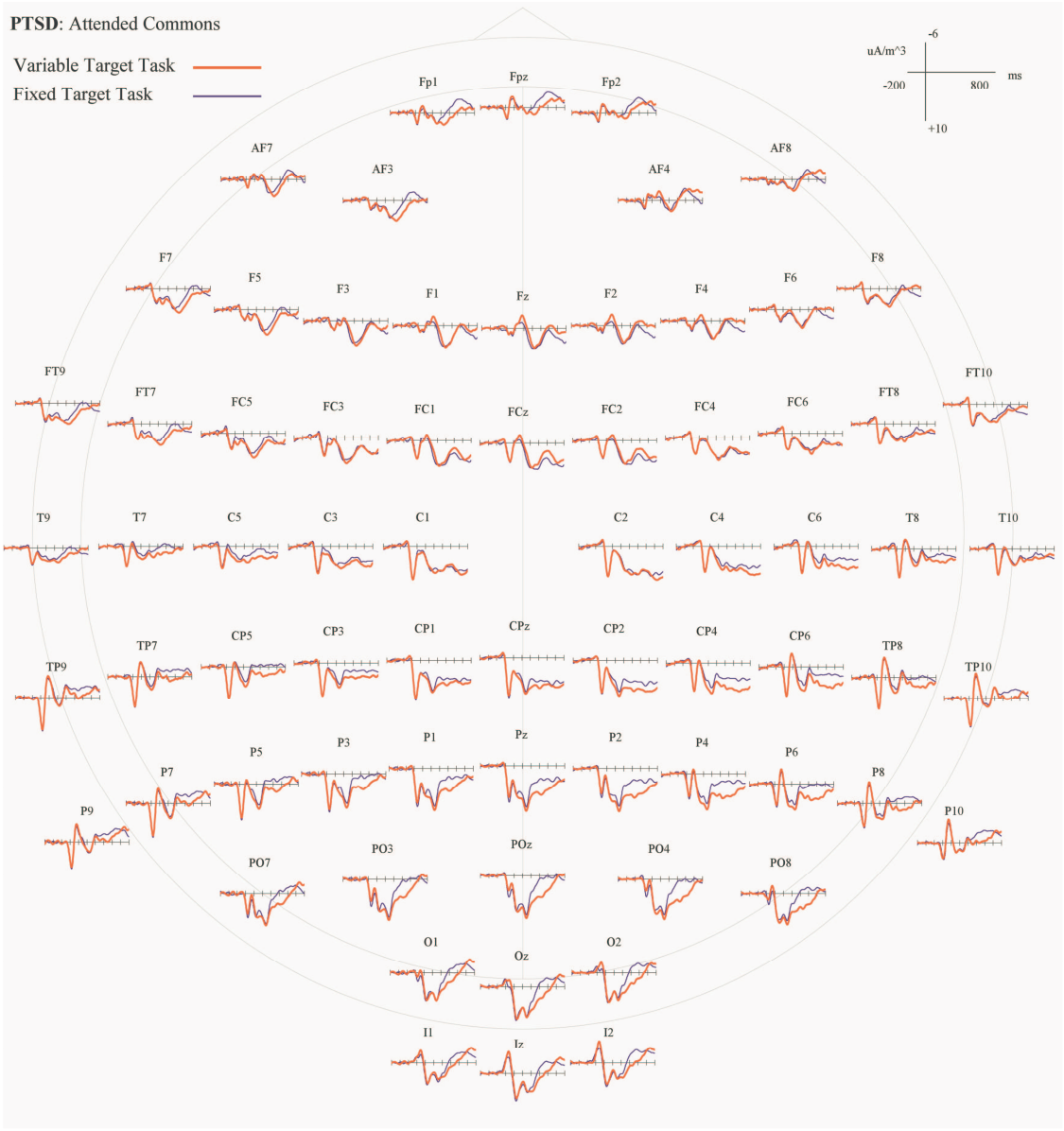

Figure 5-17. Event-related SCD in PTSD (n=10) at 70 scalp sites (-200 to 800 ms, 100 ms intervals). Attended non-target words in the variable target task elicit larger positive SCD over the posterior and prefrontal regions at 400-600 ms.

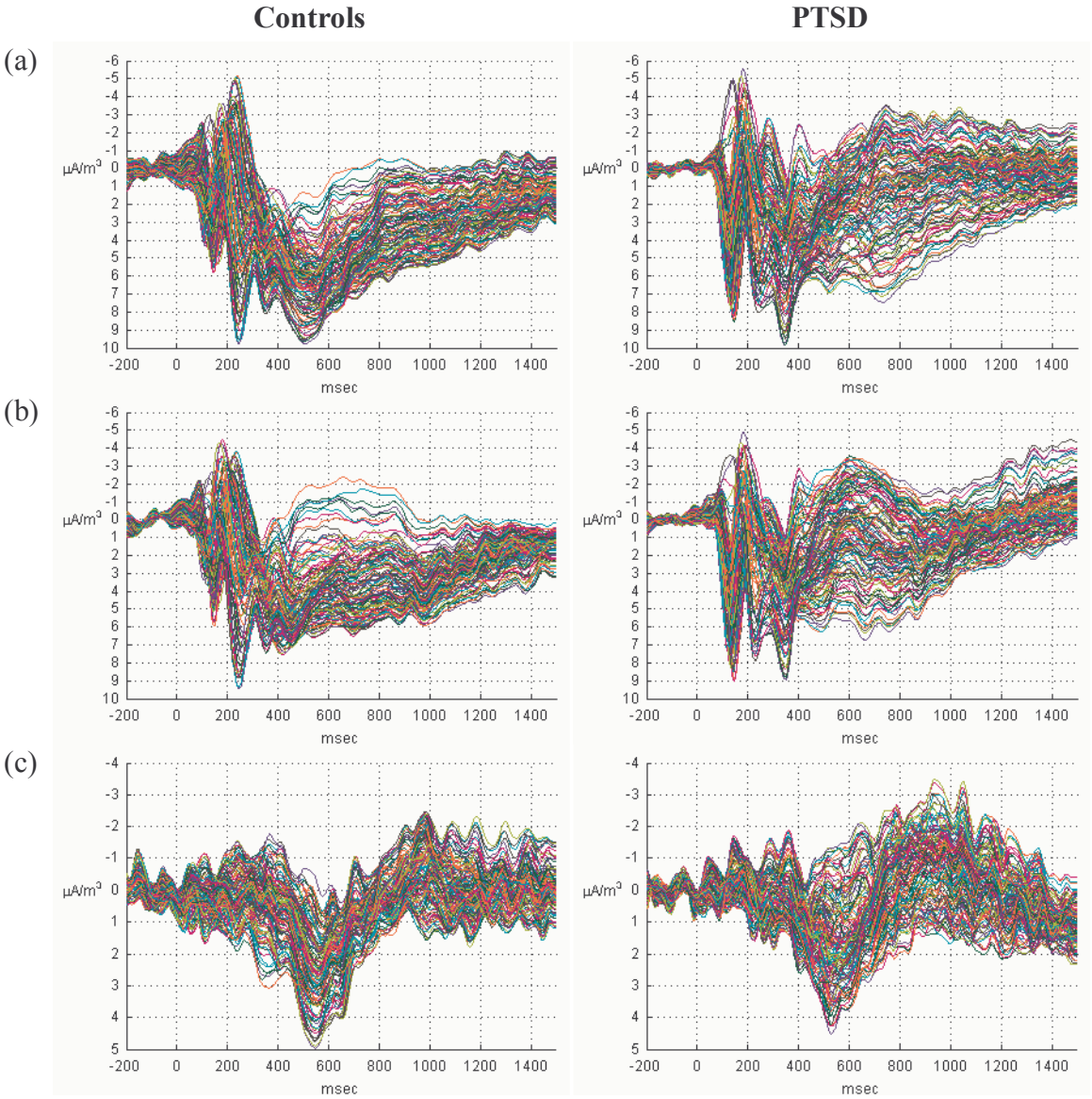

Figure 5-18. Event-related SCD waveforms at 124 scalp sites for attended common words in controls (n=10) and PTSD patients (n=10): (a) variable target task, (b) fixed target task, (c) variable - fixed.

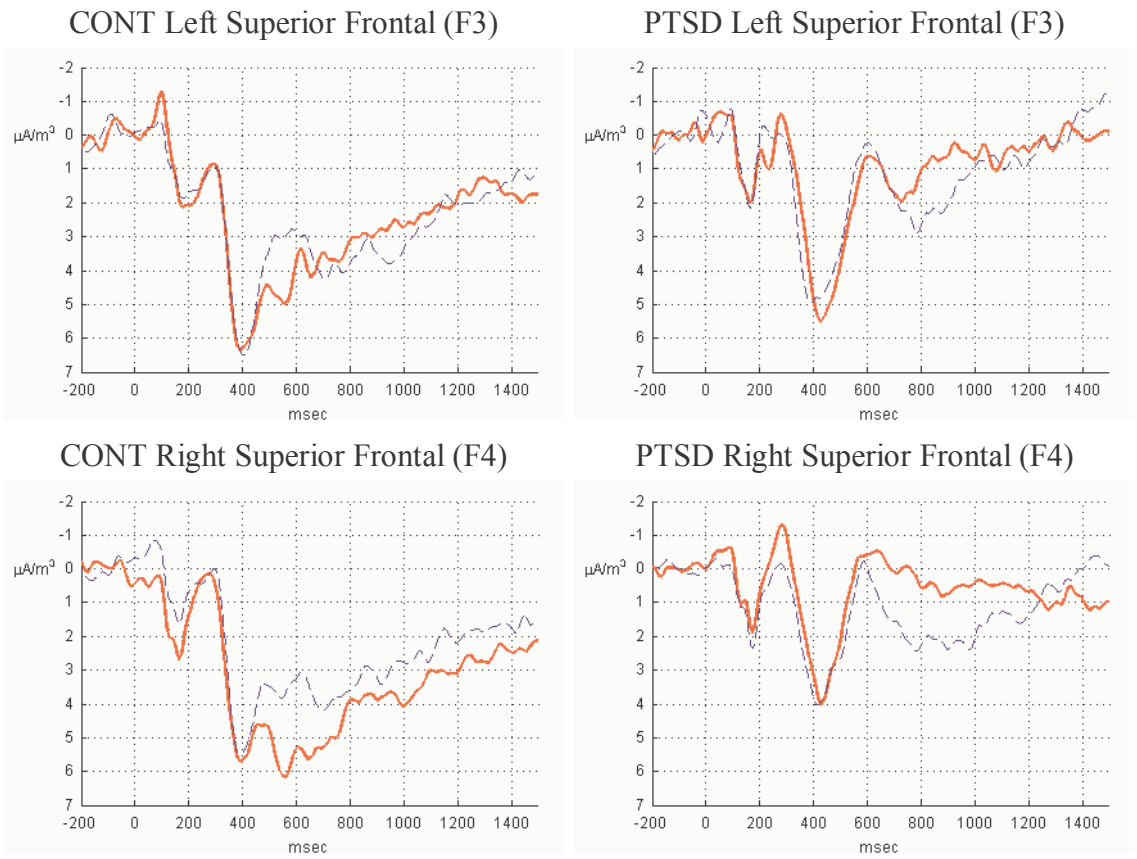

Figure 5-19. SCD for controls (n = 10) and PTSD patients (n = 10) at bilateral frontal sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the early N80 component, larger over the left than the right frontal region.

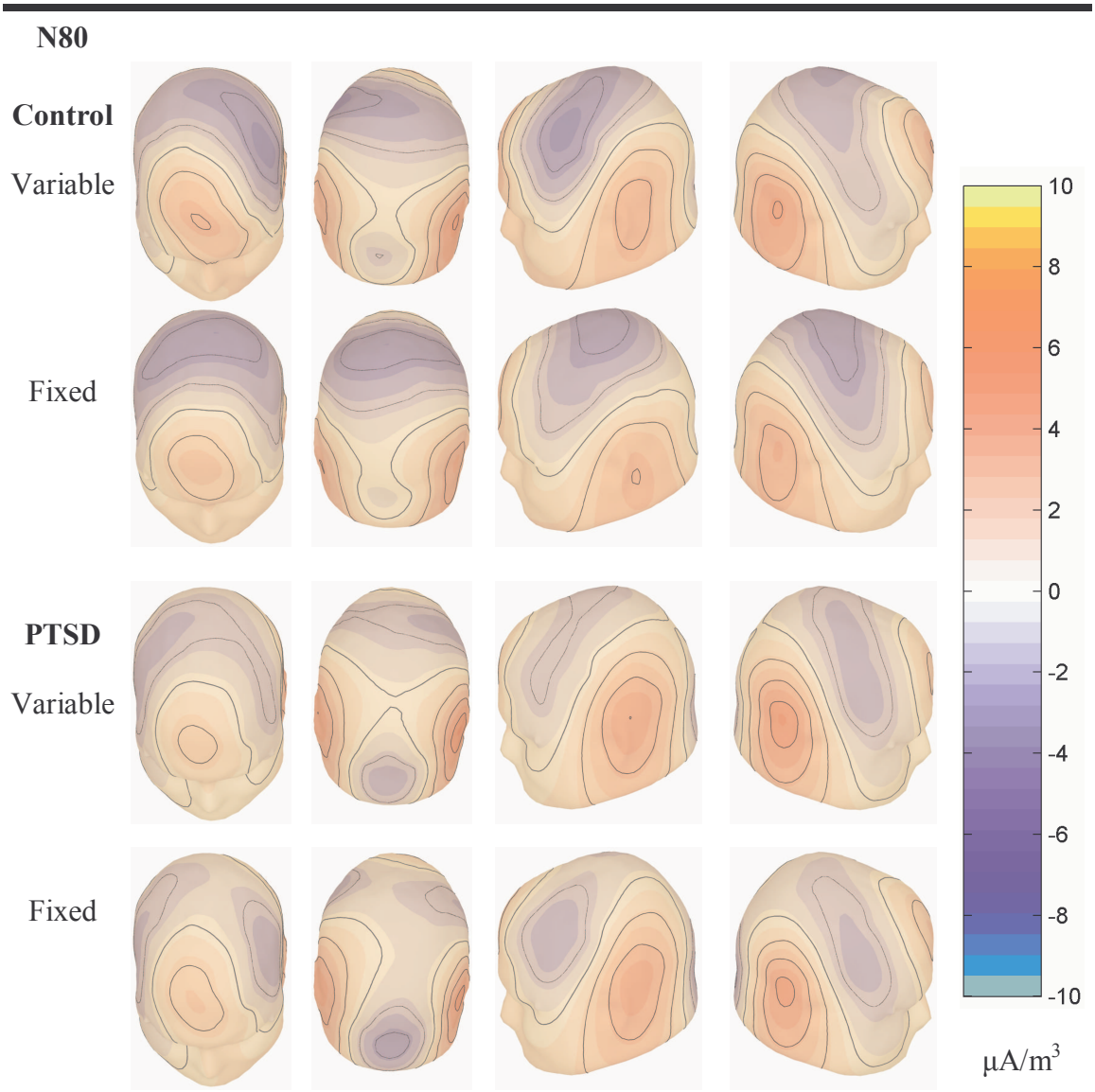

Figure 5-20. N80 SCD topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 90 ms, contours at 1 μA/m^3 intervals.

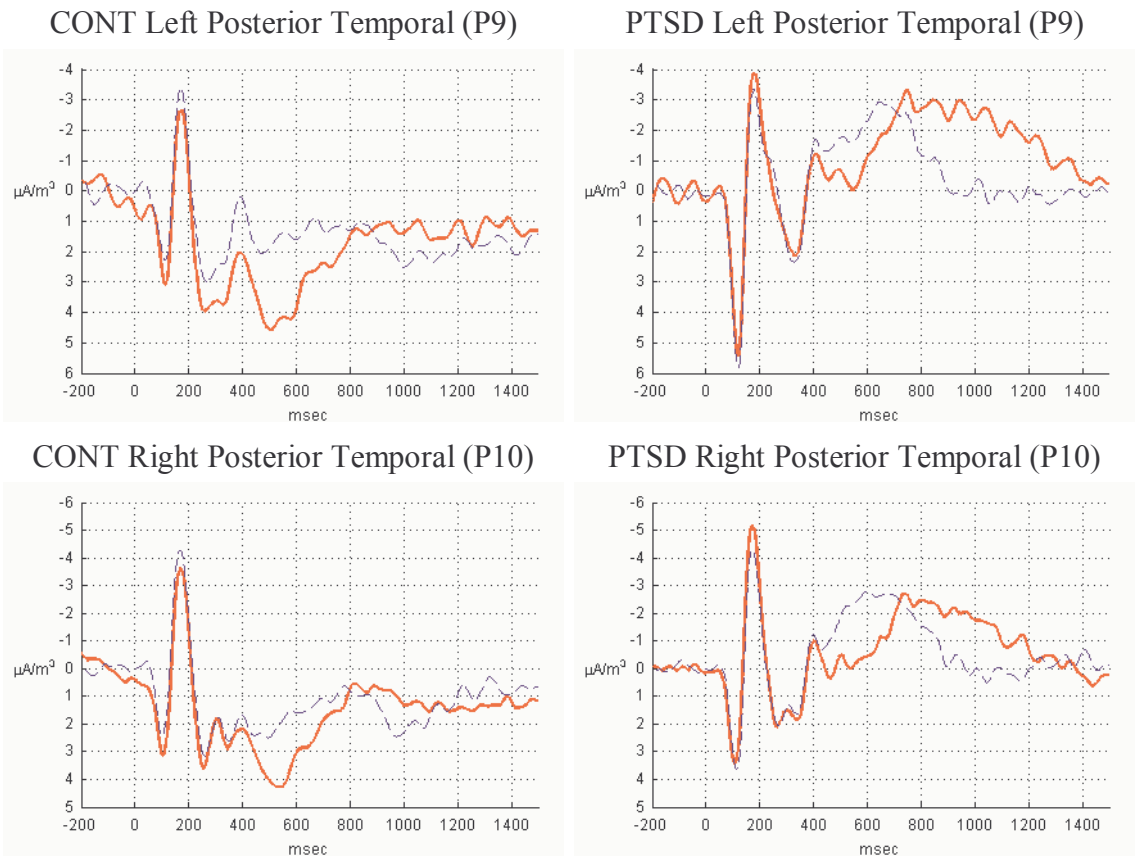

Figure 5-21. SCD for controls (n = 10) and PTSD patients (n = 10) at bilateral posterior temporal sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the early P100 component. It is largest for PTSD patients at the left posterior temporal site.

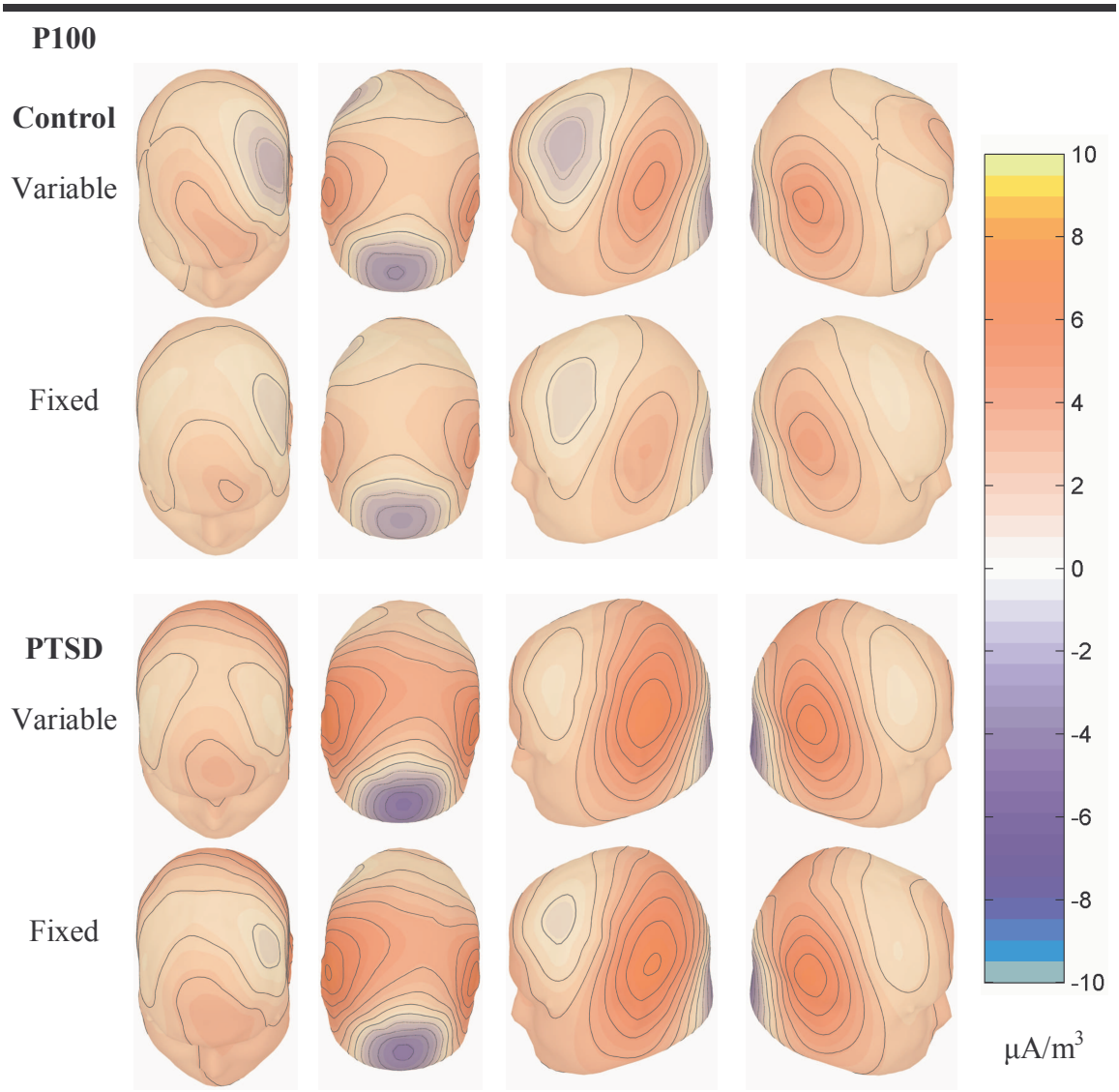

Figure 5-22. P100 SCD topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps are at 115 ms, contours at 1 μA/m^3 intervals.

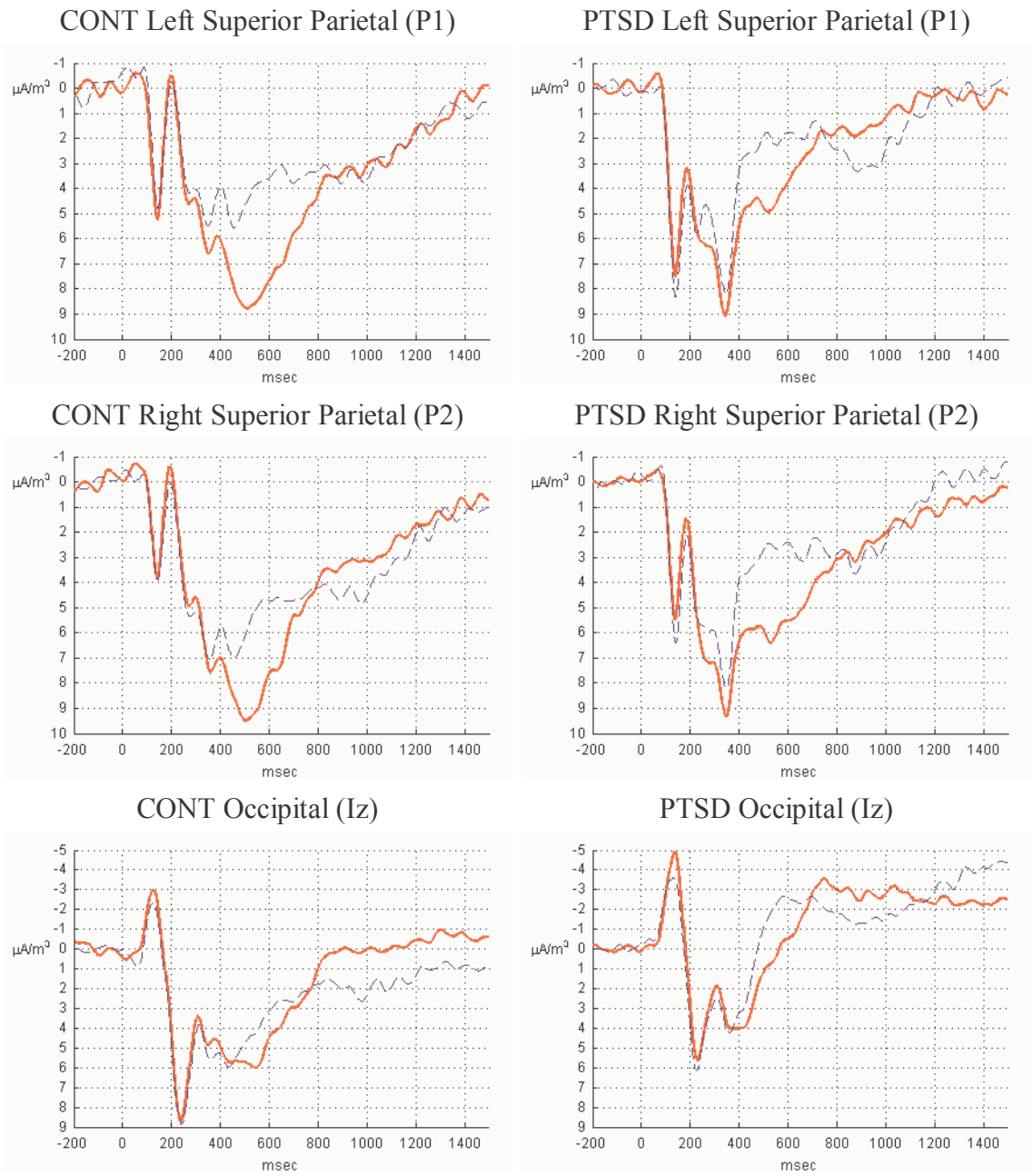

Figure 5-23. SCD for controls (n = 10) and PTSD patients (n = 10) at bilateral parietal and midline occipital sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the P150 component at parietal sites and the occipital N150 component.

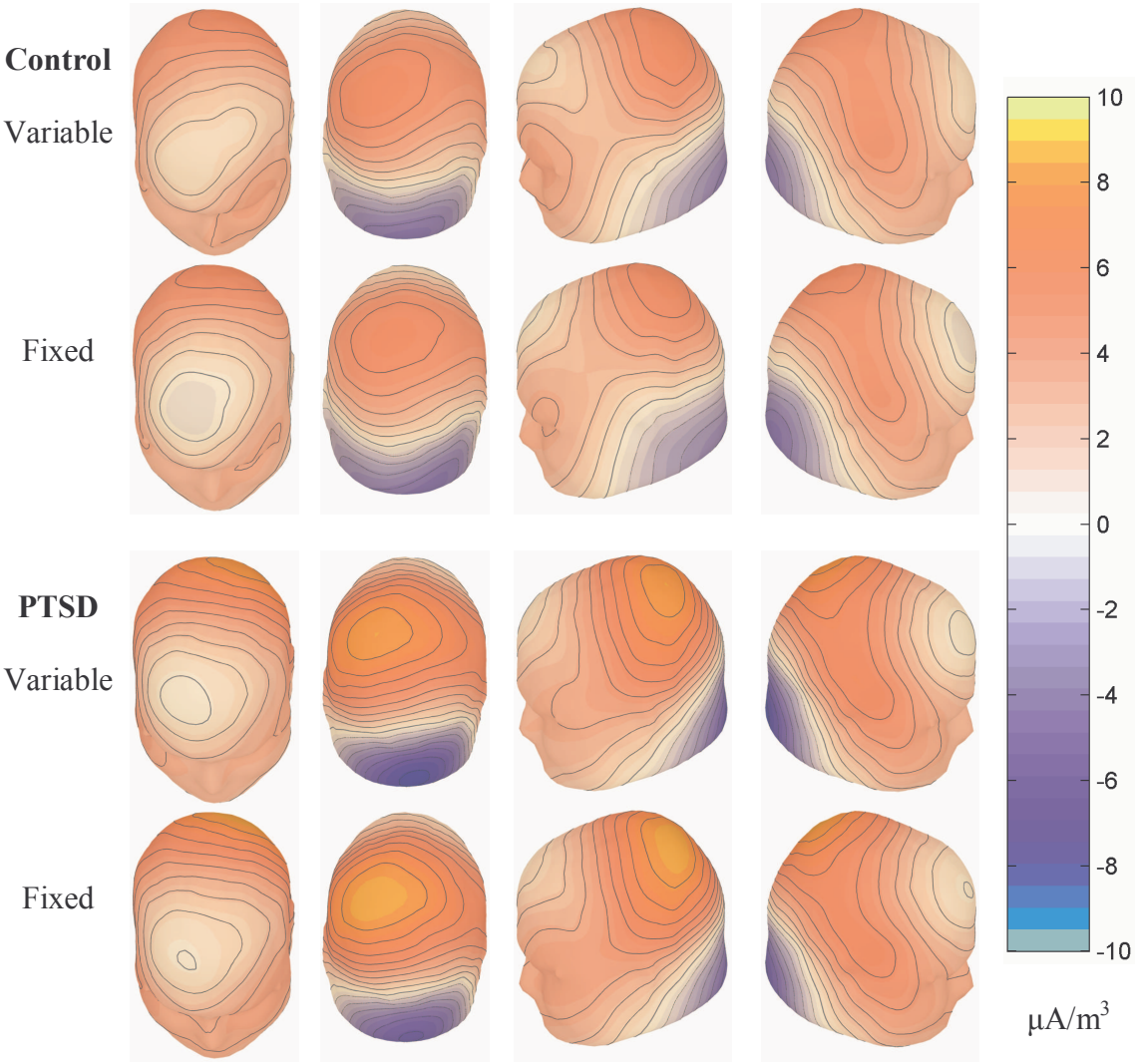

Figure 5-24. P150 & N150 SCD topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps are at 140 ms, contours at 1 μA/m^3 intervals.

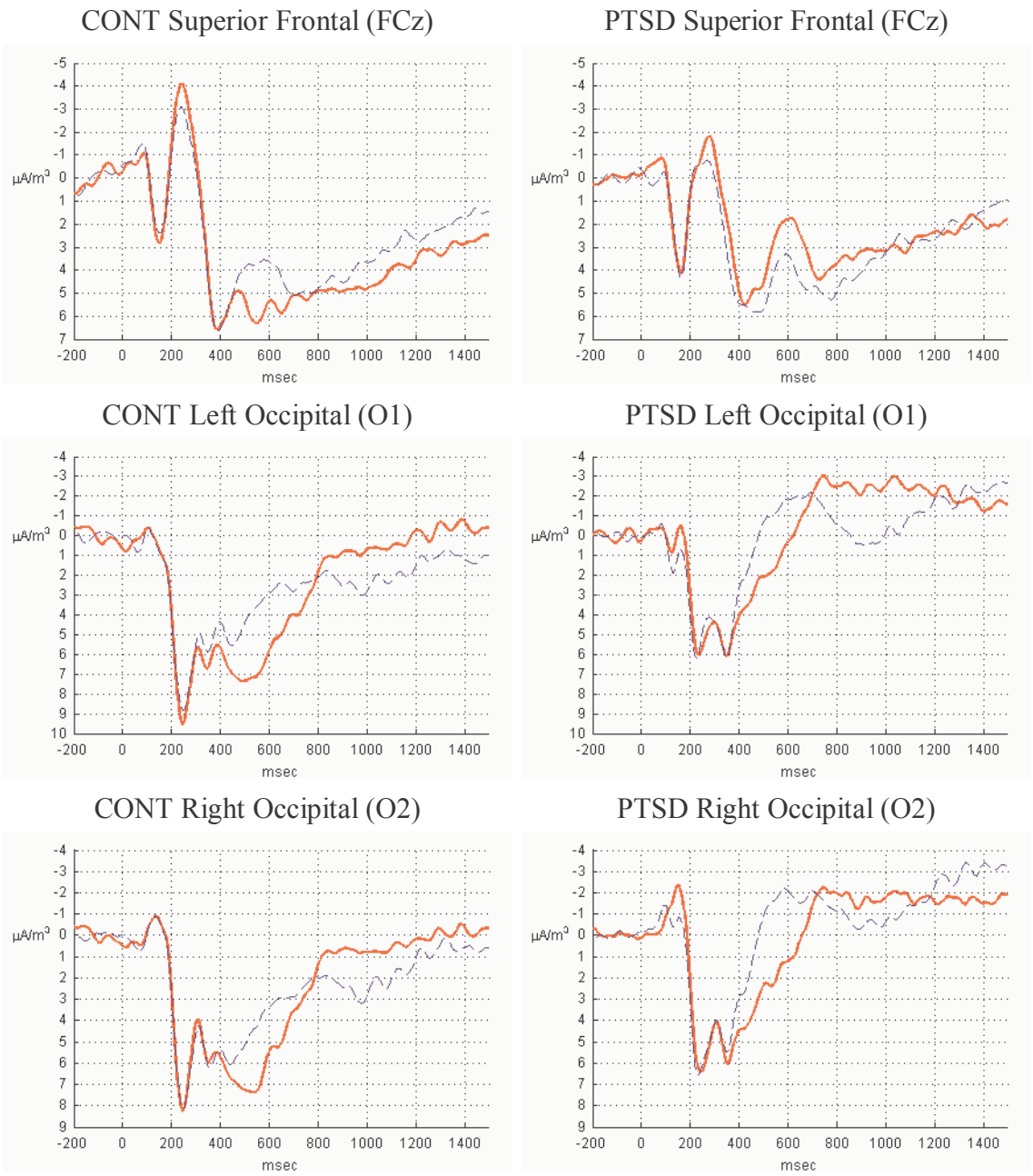

Figure 5-25. SCD for controls (n = 10) and PTSD patients (n = 10) at frontal and occipital sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the occipital P250 component and the frontal N250 component.

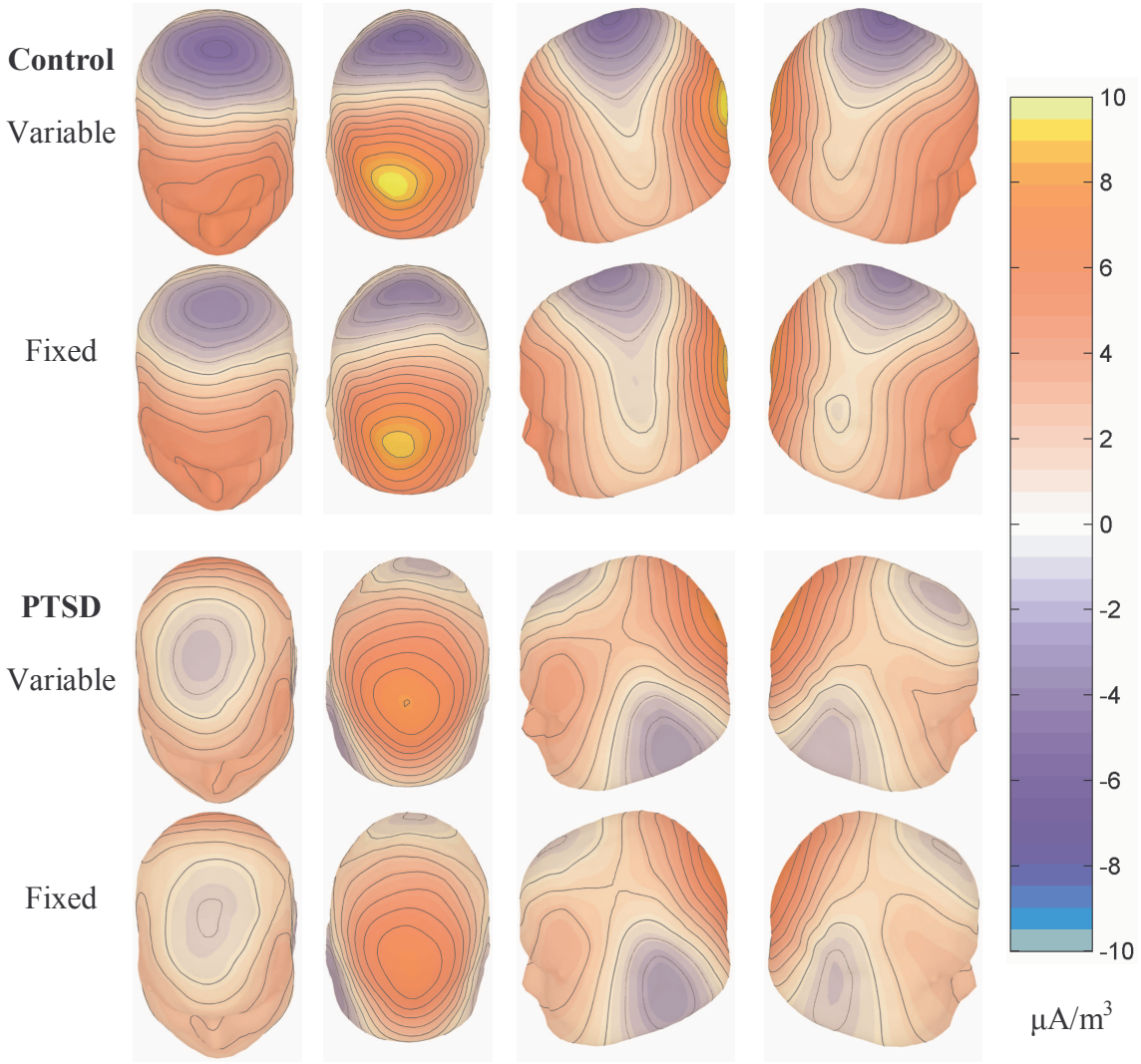

Figure 5-26. P250 & N250 SCD topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 250 ms, contours at 1 μA/m^3 intervals.

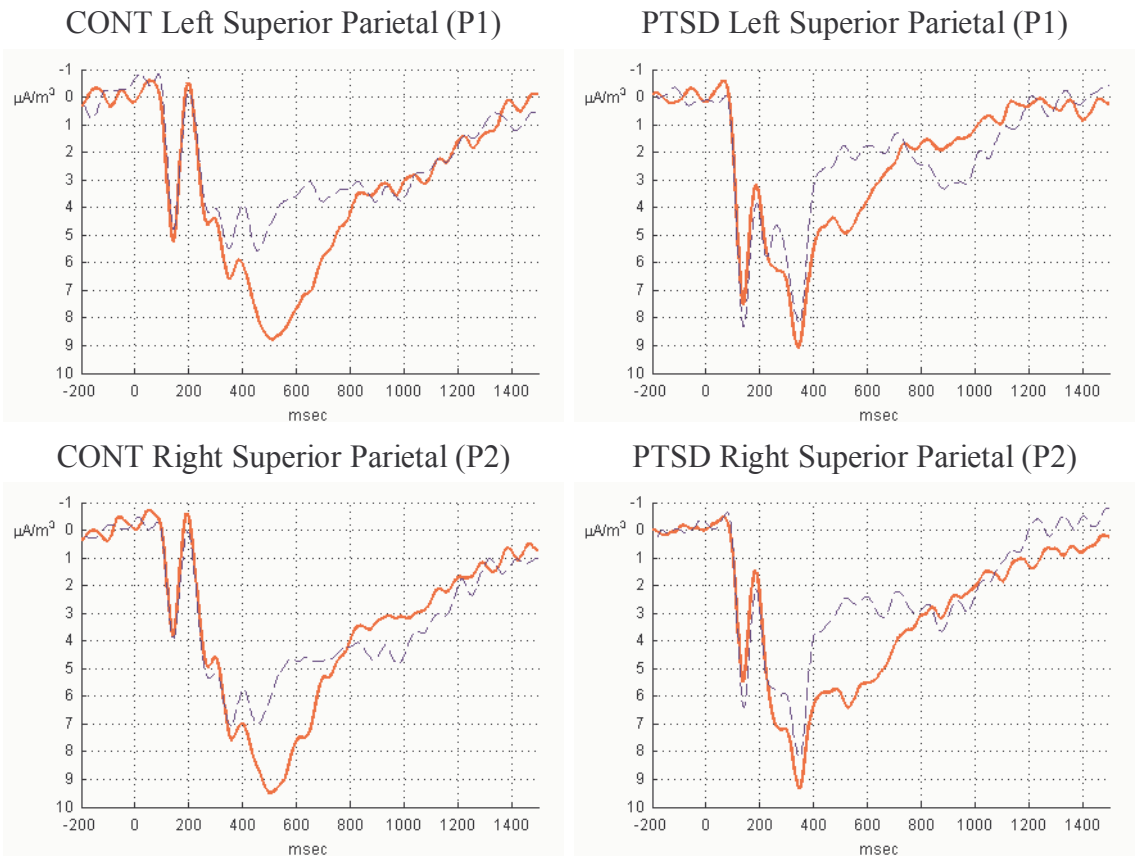

Figure 5-27. SCD for controls (n = 10) and PTSD patients (n = 10) at parietal sites for attended common words of the variable (red, solid) and fixed (blue, dash) target tasks. Note the parietal P350 followed by the P500. The conjunction of these peaks appears to be closer in controls than PTSD patients, suggesting more coherent processing to evaluate stimulus information and update working memory. There appears to be a greater delineation, even a pause, between these two processes in PTSD patients.

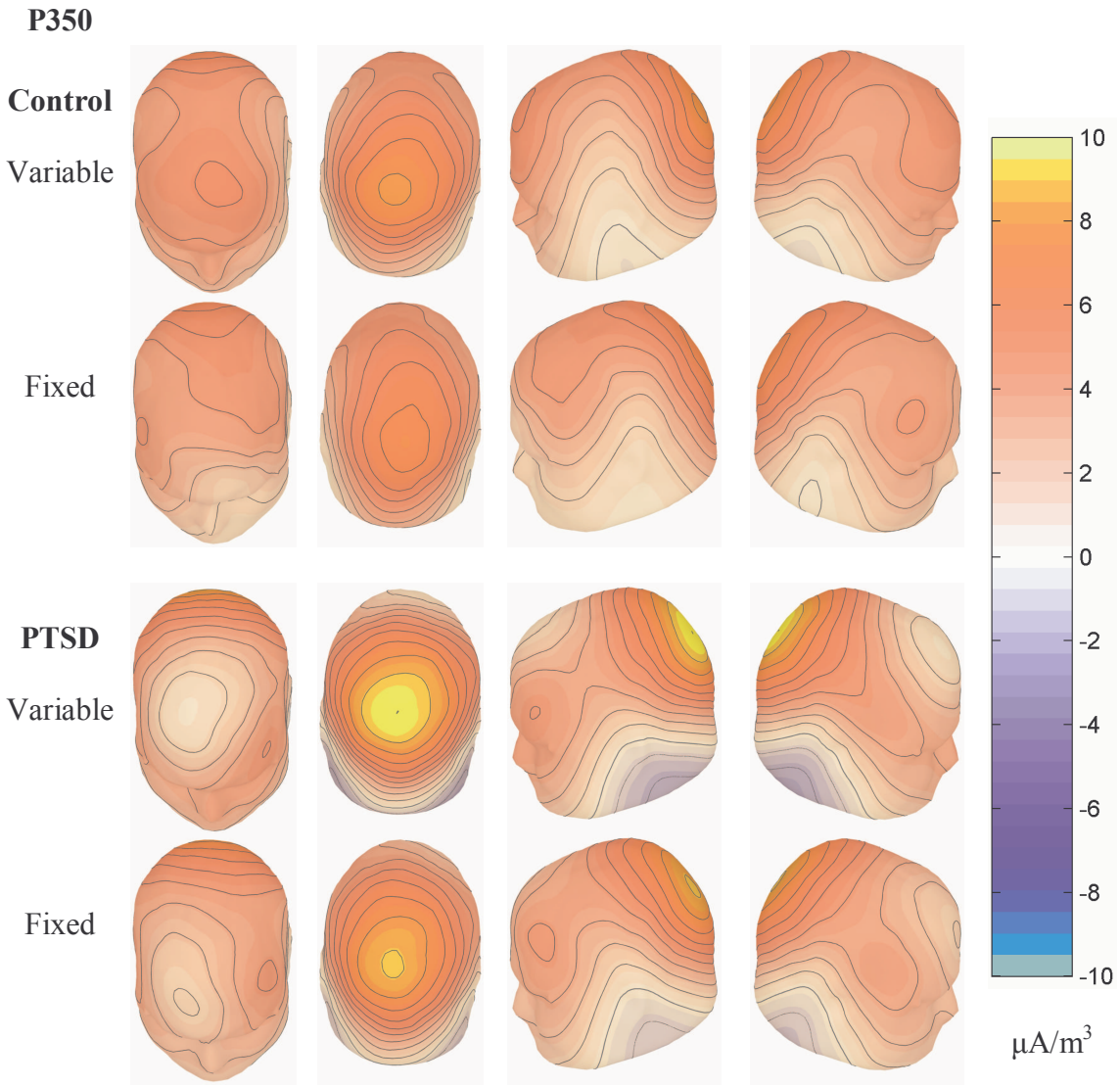

Figure 5-28. P350 SCD topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 350 ms, contours at 1 μA/m^3 intervals.

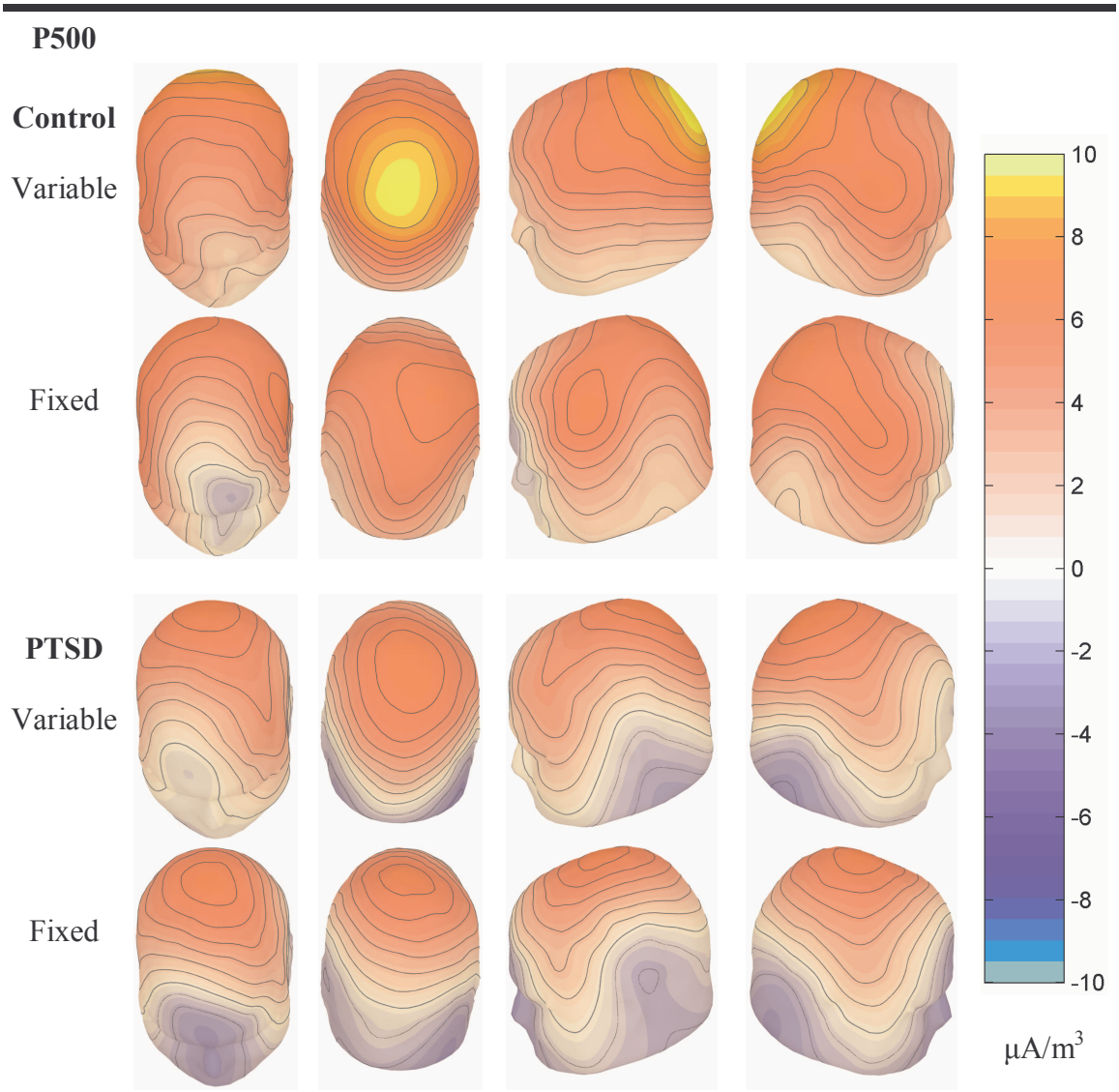

Figure 5-29. P500 SCD topography for controls (n = 10) and PTSD patients (n = 10) in working memory conditions. All maps at 500 ms, contours at 1 $\mu A/m^3$ intervals.

Table 5-6. SCD Summary Statistics for Attended Common Words in Variable and Fixed Target Tasks [a] (continued overleaf).

			Amplitude ($\mu A/m^3$)		Latency (ms)	
			CONT	PTSD	CONT	PTSD
N80	Left	V	-3.09 (1.65)	-2.00 (1.19)	90.25 (9.82)	86.75 (14.58)
SF		F	-1.94 (1.43)	-1.52 (1.42)	89.50 (7.05)	89.75 (10.64)
	Right	V	-2.16 (1.71)	-2.09 (1.21)	87.50 (8.25)	86.00 (10.55)
		F	-2.52 (1.58)	-1.32 (1.16)	87.00 (8.48)	83.50 (11.86)
P100	Left	V	6.78 (5.56)	9.75 (8.25)	117.75 (17.42)	123.75 (13.19)
PT		F	5.38 (5.80)	10.33 (9.59)	116.00 (20.01)	124.00 (13.80)
	Right	V	6.38 (3.76)	8.15 (7.83)	108.50 (17.29)	115.00 (12.47)
		F	4.98 (4.84)	8.06 (9.20)	109.00 (15.51)	114.25 (13.18)
P150	Left	V	9.23 (6.15)	12.55 (8.51)	147.00 (25.79)	141.00 (23.34)
SP		F	8.07 (6.71)	12.99 (9.54)	142.75 (19.81)	141.50 (23.55)
	Right	V	7.84 (5.55)	11.27 (8.23)	144.25 (26.12)	137.25 (20.96)
		F	6.96 (5.47)	11.63 (9.51)	138.50 (18.23)	138.50 (24.19)
N150	Left	V	-6.57 (5.19)	-6.53 (10.11)	122.25 (34.73)	129.50 (26.45)
OC		F	-6.13 (4.31)	-5.91 (11.16)	120.75 (35.63)	131.50 (26.04)
	Right	V	-6.87 (4.83)	-10.24 (7.20)	144.00 (38.79)	150.25 (26.15)
		F	-6.50 (3.95)	-6.25 (11.59)	141.50 (38.36)	144.25 (21.41)

[a] V = variable target task, attended common words; F = fixed target task, attended common words; CONT, n = 10; PTSD, n = 10; values are mean (SD).

Table 5-6 (continued). SCD Summary Statistics for Common Words in Variable and Fixed Target Tasks [a]

			Amplitude ($\mu A/m^3$)		Latency (ms)	
			CONT	PTSD	CONT	PTSD
P250	Left	V	11.52 (5.74)	10.51 (7.65)	247.00 (24.97)	253.00 (37.30)
OC		F	10.76 (5.02)	9.36 (8.08)	245.25 (21.36)	250.25 (35.50)
	Right	V	11.27 (3.67)	9.33 (8.03)	247.50 (29.44)	252.75 (28.85)
		F	10.66 (3.87)	8.36 (8.01)	244.00 (21.67)	245.25 (25.34)
N250	Left	V	-6.22 (2.83)	-2.85 (5.66)	243.75 (21.64)	245.00 (31.62)
SF		F	-4.75 (2.10)	-2.71 (5.00)	233.25 (27.03)	243.00 (30.70)
	Right	V	-6.51 (3.55)	-3.33 (5.33)	242.75 (18.65)	234.50 (26.50)
		F	-4.85 (3.35)	-2.28 (4.50)	241.00 (23.37)	232.00 (31.86)
P350	Left	V	10.43 (5.52)	12.58 (8.63)	353.75 (22.74)	346.75 (22.94)
SP		F	9.21 (5.47)	10.17 (7.83)	355.00 (18.22)	352.50 (16.75)
	Right	V	10.98 (5.81)	12.92 (8.81)	356.00 (19.55)	349.00 (20.21)
		F	10.05 (5.62)	10.67 (7.83)	355.25 (17.93)	348.75 (16.51)
P500	Left	V	13.44 (4.89)	8.77 (6.00)	498.25 (50.03)	512.50 (67.30)
SP		F	8.74 (3.60)	5.57 (5.65)	486.75 (33.73)	494.25 (47.43)
	Right	V	13.35 (5.25)	9.94 (5.94)	512.25 (53.38)	508.75 (44.97)
		F	8.87 (3.68)	6.63 (5.51)	506.00 (42.40)	505.50 (58.28)

[a] V = variable target task, attended common words; F = fixed target task, attended common words; CONT, n = 10; PTSD, n = 10; values are mean (SD).

Table 5-7. Inferential Statistics for Working Memory SCD Components [a]

SCD		GP	WM	GPxWM	HS	GPxHS	WMxHS	GPxWMxHS
N80	Amp	1.80	4.72*	0.23	0.23	0.07	2.82	6.21*
SF	Lat	0.43	0.01	0.04	2.26	0.05	0.66	0.79
P100	Amp	1.06	2.59	5.24*	3.47	1.50	0.98	1.00
PT	Lat	1.26	0.22	0.04	5.39*	0.02	0.16	1.08
P150	Amp	1.50	0.40	2.11	9.39**	0.01	0.06	0.20
SP	Lat	0.13	0.63	1.28	8.79**	0.00	0.15	1.39
N150	Amp	0.05	1.64	0.80	3.18	1.63	1.38	1.49
OC	Lat	0.38	1.45	0.00	4.88*	0.07	3.22	1.95
P250	Amp	0.35	5.01*	0.24	1.14	0.59	0.15	0.00
OC	Lat	0.16	3.06	0.32	0.06	0.03	1.22	0.26
N250	Amp	2.47	7.24*	1.47	0.05	0.03	5.19*	2.21
SF	Lat	0.02	1.38	0.30	1.23	4.52*	0.46	0.57
P350	Amp	0.22	7.72*	1.05	1.06	0.06	0.44	0.04
SP	Lat	0.60	0.17	0.12	0.03	0.56	0.63	0.16
P500	Amp	2.51	51.65***	1.49	0.80	0.74	0.01	0.14
SP	Lat	0.07	0.96	0.01	1.57	0.63	0.59	0.14

[a] Values are F[1,18], GP = group, WM = working memory, HS = hemisphere.

* p<.05, ** p<.01, *** p<.001, *2-tailed*; † p<.05, †† p<.01, ††† p<.001, *1-tailed*.

5.4.5.2 N80 SCD

N80 SCD peak amplitude was measured between 60-105 ms, with the largest amplitude in the superior frontal region at 85-95 ms (see Figure 5-20 & Table 5-6). ANOVA indicated a significant three-way interaction of group by working memory by hemisphere in N80 amplitude (see Table 5-7). The mean N80 peak amplitude was larger for the variable than the fixed target task (M = -0.51 μA/m^3, SE = 0.23 μA/m^3, p<.05). The interaction comprised larger left superior frontal N80 for the variable than the fixed target task in controls (M = -1.15 μA/m^3, SE = 0.35 μA/m^3, p<.01).

5.4.5.3 P100 SCD

P100 SCD peak amplitude was measured between 80-140 ms, with the largest amplitude in the posterior temporal region at 105-125 ms (see Figure 5-22 & Table 5-6). ANOVA indicated a significant interaction of group by working memory in P100 amplitude (see Table 5-7). There was a larger P100 peak for the variable than the fixed target task in controls (M = 1.40 μA/m^3, SE = 0.51 μA/m^3, p<.05), but not in PTSD (M = -0.24 μA/m^3, SE = 0.51 μA/m^3, *ns*). Also, ANOVA indicated a significant hemisphere effect in P100 peak latency (see Table 5-7). The P100 peak arose later over the left than the right posterior temporal region (M = 8.69 ms, SE = 3.74 ms, p<.05).

5.4.5.4 P150 SCD

P150 SCD peak amplitude was measured between 80-200 ms, with the largest amplitude in the superior parietal region at 135-150 ms (see Figure 5-24 & Table 5-6). ANOVA indicated a significant main effect of hemisphere in P150 amplitude and latency (see Table 5-7). The mean P150 peak amplitude was larger over the left than the right superior parietal region (M = 1.29 μA/m^3, SE = 0.42 μA/m^3, p<.01). Also, the mean P150 SCD peak latency was later over the left than the right superior parietal region (M = 3.44 ms, SE = 1.16 ms, p<.01).

5.4.5.5 N150 SCD

N150 SCD peak amplitude was measured between 80-200 ms, with the largest amplitude in the occipital region at 120-155 ms (see Figure 5-24 & Table 5-6). ANOVA indicated a significant hemisphere difference in N150 latency (see Table 5-7). The N150 SCD mean peak latency was shorter over the left than the right occipital region (M = -19.00 ms, SE = 8.60 ms, p<.05).

5.4.5.6 P250 SCD

P250 SCD peak amplitude was measured between 200-320 ms, with the largest amplitude in the occipital region at 240-255 ms (see Figure 5-26 & Table 5-6). ANOVA indicated a significant working memory effect in P250 amplitude (see Table 5-7). The mean P250 peak amplitude was larger in the variable than the fixed target task (M = 0.87 μA/m^3, SE = 0.39 μA/m^3, p<.05).

5.4.5.7 N250 SCD

N250 SCD peak amplitude was measured between 180-300 ms, with the largest amplitude in the superior frontal region at 230-245 ms (see Figure 5-26 & Table 5-6). ANOVA indicated a significant interaction of working memory by hemisphere in N250 amplitude (see Table 5-7). The mean N250 peak amplitude was larger for the variable than the fixed target task over the right superior frontal region (M = -1.35 μA/m^3, SE = 0.39 μA/m^3, p<.01). Also, ANOVA indicated a significant group by hemisphere interaction in N250 latency (see Table 5-7). The mean N250 peak latency was longer over the left than the right superior frontal region in PTSD (M = 10.75 ms, SE = 4.70 ms, p<.05), but not in controls (M = -3.38 ms, SE = 4.70 ms, *ns*).

It is noteworthy that the mean comparisons for the N250 peak amplitude indicate a significant group by working memory interaction, although the F statistic is not significant. As there was no specific hypothesis for this effect, strict standards of reporting would dismiss this result, but it is given here as an aside. The mean N250 peak amplitude was greater in the variable target task for controls (M = -1.56 μA/m^3, SE = 0.57 μA/m^3, p<.05), but not for patients (M = -0.59 μA/m^3, SE = 0.57 μA/m^3, *ns*). This result is not considered any further in this report.

5.4.5.8 P350 SCD

P350 SCD peak amplitude was measured between 300-400 ms, with the largest amplitude in the superior parietal region at 345-360 ms (see Figure 5-28 & Table 5-6). ANOVA indicated a significant working memory effect in P350 amplitude (see Table 5-7). The mean P350 peak amplitude was larger for the variable than the fixed target task over the superior parietal regions (M = 1.70 μA/m^3, SE = 0.61 μA/m^3, p<.05).

5.4.5.9 P500 SCD

P500 SCD peak amplitude was measured between 400-600 ms, with the largest amplitude in the superior parietal region at 485-515 ms (see Figure 5-29 & Table 5-6). ANOVA indicated a significant working memory effect in P500 amplitude (see Table 5-7). The mean P500 peak amplitude was larger for the variable than the fixed target task (M = 3.92 μA/m^3, SE = 0.55 μA/m^3, p<.001).

5.4.5.10 Summary of SCD Findings

Significant differences were found in the following SCD components:

- at 90-95 ms, controls had a left superior frontal N80 that was larger in the working memory updating condition,
- at 105-125 ms, controls had a posterior temporal P100 that was larger in the working memory updating condition and the P100 arose later over the left than the right posterior temporal region,
- at 120-150 ms, a P150 was larger and later over the left than the right superior parietal region and an N150 was earlier over the left than the right occipital region,
- at 230-255 ms, an occipital P250 and a right superior frontal N250 were larger in the working memory updating condition and PTSD patients had a delay in the N250 over the left superior frontal region, and

- at 345-360 ms and 485-515 ms, a superior parietal P350 and P500, respectively, were larger in the working memory updating condition.

5.4.6 SCD Difference Waves

The working memory difference waves demonstrate larger working memory updating activity for controls than PTSD patients at several posterior and frontal regions at 400-800 ms (see Figure 5-18 and Figure 5-30 to Figure 5-32). The components identified for further analysis were a negative peak at 350 ms (ND350) and a large positive peak at 550 ms (PD550). The summary statistics for these components are given in Table 5-8 and the inferential statistics are described below (see Table 5-9), with the mean differences for significant effects.

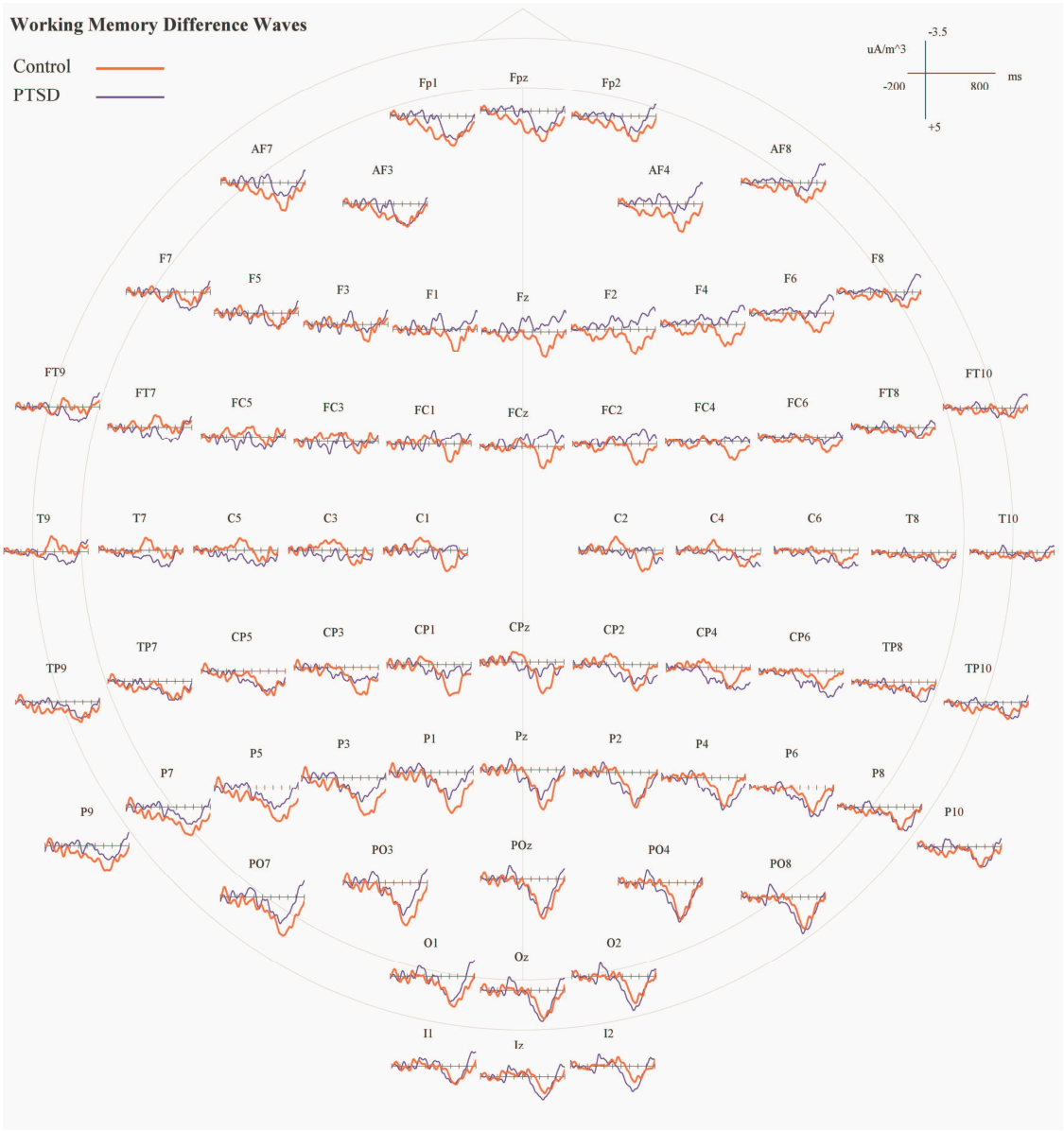

Figure 5-30. Working memory SCD difference waves in controls (n=10) and PTSD patients (n=10) at 70 scalp sites (-200 to 800 ms, 100 ms intervals). The controls demonstrate larger working memory updating activity over left posterior temporal, left parietal and fronto-central regions at 500-700 ms.

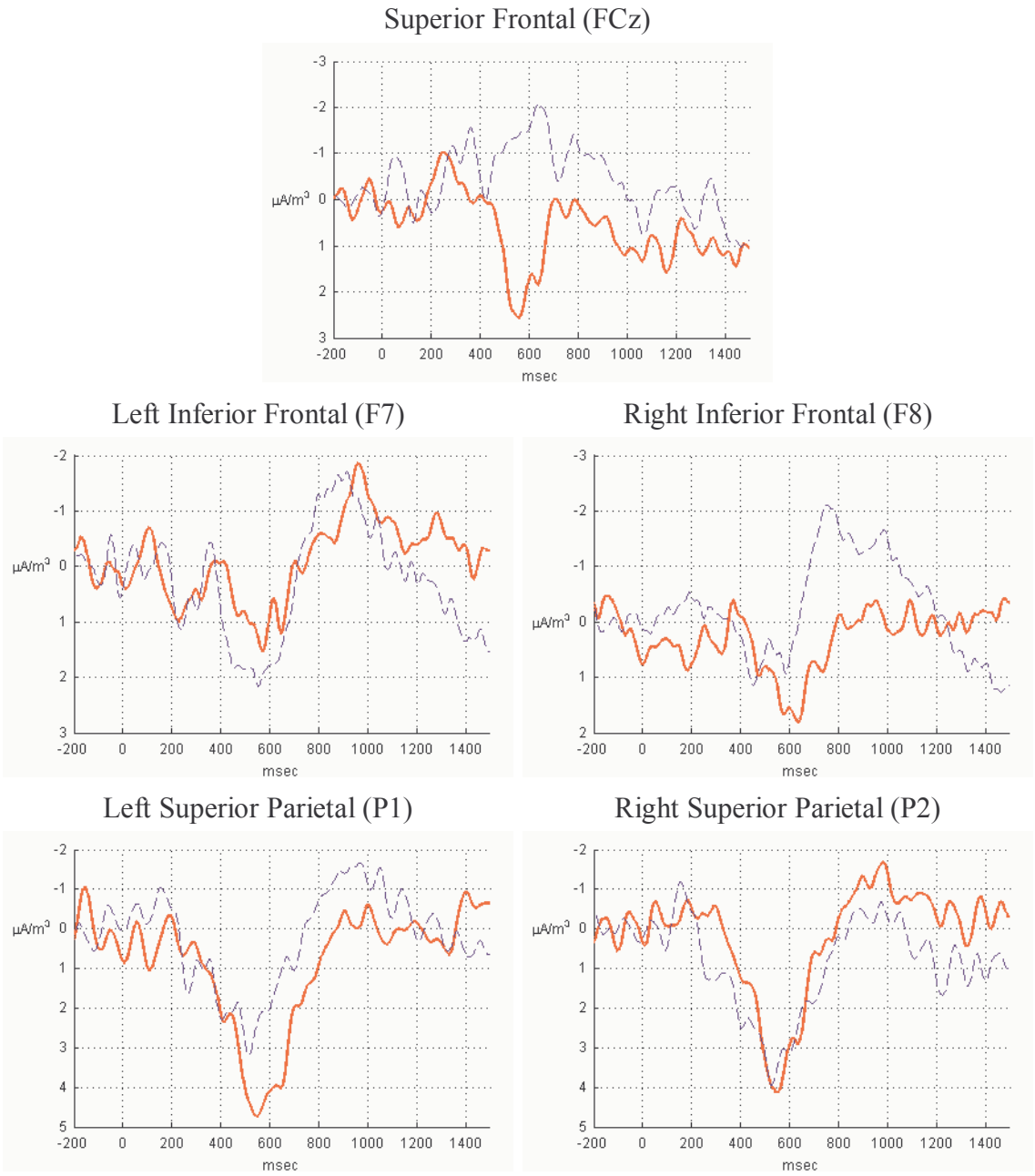

Figure 5-31. SCD working memory difference waves for controls (n = 10; red, solid) and PTSD patients (n = 10; blue, dash). Note the small frontal ND350 component and the larger frontal and parietal PD550 component.

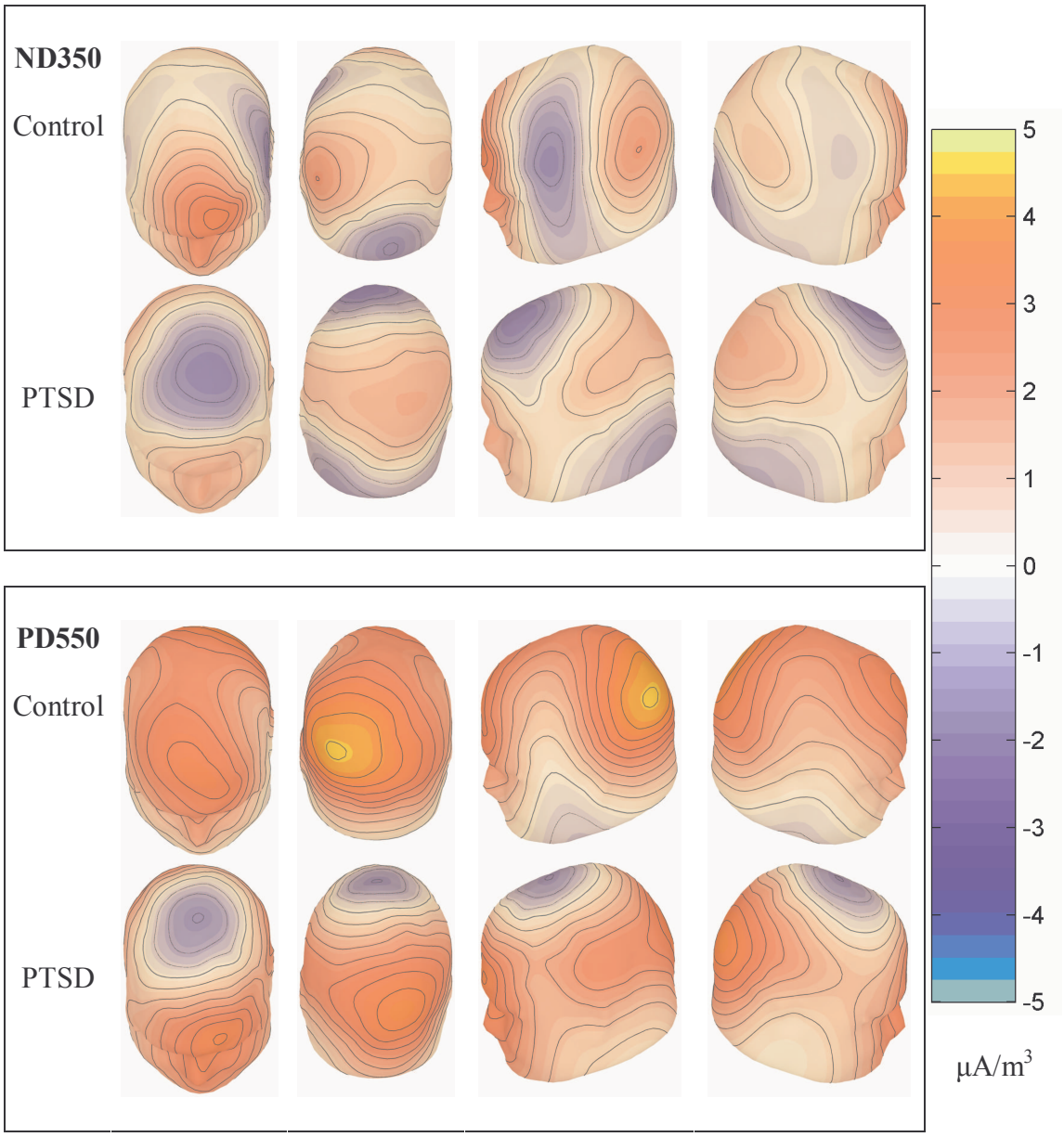

Figure 5-32. ND350 & PD550 SCD topography for controls (n = 10) and PTSD patients (n = 10) for the working memory difference wave (contours at 0.5 $\mu A/m^3$ intervals). The ND350 is given at 370 ms and the PD550 is given at 580 ms.

Table 5-8. Summary Statistics for Working Memory SCD Difference Components [a]

		Amplitude ($\mu A/m^3$)		Latency (ms)	
		CONT	PTSD	CONT	PTSD
ND350	SF Left	-3.00 (3.12)	-3.57 (3.56)	371.75 (43.78)	357.25 (31.52)
	SF Right	-2.57 (2.59)	-3.10 (3.69)	380.75 (42.93)	359.75 (35.60)
PD550	SP Left	7.20 (2.61)	5.08 (2.43)	588.25 (58.42)	581.50 (62.90)
	SP Right	6.05 (2.82)	6.12 (1.64)	563.75 (50.54)	563.00 (68.69)
	SF Left	4.18 (1.97)	2.63 (2.26)	584.75 (55.93)	554.75 (73.19)
	SF Right	4.13 (2.58)	1.35 (2.20)	583.00 (59.49)	565.50 (55.86)

[a] CONT, n = 10; PTSD, n = 10; values are mean (SD).

Table 5-9. Inferential Statistics for Working Memory SCD Difference Components [a]

ERP		GP	HS	GPxHS
ND350	Amp	0.17	0.64	0.00
SF	Lat	1.55	0.34	0.11
PD550	Amp	1.02	0.02	8.35**
SP	Lat	0.02	4.41	0.09
PD550	Amp	6.15*	1.68	1.43
SF	Lat	1.23	0.07	0.13

[a] Values are $F[1,18]$, GP = group, HS = hemisphere.

* $p<.05$, ** $p<.01$, *** $p<.001$, *2-tailed*; † $p<.05$, †† $p<.01$, ††† $p<.001$, *1-tailed*.

5.4.6.1 ND350 SCD

The ND350 peak was located between 300-450 ms, with largest amplitude over the superior frontal region at 355-385 ms (see Figure 5-32 & Table 5-8). ANOVA indicated no significant differences (see Table 5-9).

5.4.6.2 PD550 SCD

The PD550 peak was located between 450-700 ms, with largest amplitude over the superior parietal and frontal regions at 550-590 ms (see Figure 5-32 & Table 5-8). The PD550 component arose from larger positive potentials at 450-700 ms for the variable than fixed target task (see Figure 5-18). PD550 peak amplitude was greatest

over posterior regions and specific hypothesis warranted analysis at the superior frontal region also.

Superior parietal: ANOVA indicated a significant group by hemisphere interaction in PD550 amplitude (see Table 5-9). The PD550 mean amplitude was larger for controls than PTSD patients, over the left hemisphere (M = 2.12 μA/m^3, SE = 1.13 μA/m^3, p<.05, *1-tailed*). There was also a larger PD550 mean amplitude over the left than the right superior parietal area in controls (M = 1.14 μA/m^3, SE = 0.53 μA/m^3, p<.05).

Superior frontal: ANOVA indicated a significant group difference in PD550 amplitude (see Table 5-9). The superior frontal PD550 was larger for controls than PTSD patients (M = 2.17 μA/m^3, SE = 0.87 μA/m^3, p<.05).

5.4.6.3 Summary of SCD Difference Component Findings

At 550-590 ms, a PD550 was larger for controls than PTSD patients, over the left superior parietal region and the superior frontal region.

5.5 DISCUSSION

5.5.1 Overview

This study has demonstrated activity related to working memory updating, primarily in frontal and parietal areas at 400-800 ms. The frontal and parietal components, which were clearly illustrated in the difference waves, demonstrate abnormal activity in PTSD patients.

The previous chapter examined the initial selection and evaluation of attended words, which involved comparison with a target representation. This study has demonstrated enhanced activity during the updating of the target representation. The previous chapter illustrates stimulus selection and evaluation processes within

300-600 ms. Activity related to working memory updating is clearly apparent in this study at 400-800 ms, in addition to the activity observed during stimulus evaluation alone.

There were deficits for PTSD patients in these working memory components, including delayed superior frontal P400 ERP, smaller parietal P550 ERP, and smaller frontal and parietal activity for the PD550 ERP. Combined with deficits in stimulus evaluation, this pattern of deficits indicates (a) poor integration of new information into working memory and/or (b) a deficit in the sustained attention and retention of the new information in working memory. These processes are critical for adaptive action.

5.5.2 Working Memory Updating

There are indications of early visual modulation related to working memory in the posterior temporal P90 ERP (P100 SCD), occipital N150 ERP and frontal P150 ERP. The enhanced activity could indicate greater resource allocation for active, controlled stimulus processing (Baddeley, 1992). These effects may reflect the early engagement of attention processes in a distributed neural network, involving links between early sensory areas and the frontal executive systems. The functional connections between frontal executive systems and posterior stimulus processing areas may provide for modulation of sensory processing, including enhanced sensory activation during controlled working memory processing. Such early modulation of sensory processing is not commonly reported in working memory studies and it was not expected that the ERP activity of this study would demonstrate these effects. For example, Gevins et al. (1996) did not report any significant differences in early occipital P1 or N1 activity for spatial or verbal working memory processes. The earliest activity to indicate working memory effects in their study was a vertex P200 that was larger during working memory activity, especially spatial working memory; there were no clear indications of frontal activity during early stages of visual processing. That study did not report an

extensive analysis of topographic activity, rather it focused on specific regions of interest. However, a recent high resolution ERP study of visual processing clearly indicates that frontal executive systems are engaged during early visual processing (Foxe & Simpson, 2002). The linguistic information of the present study may demand more cognitive resources than previous working memory studies for simple visual features. It is difficult to precisely identify the cortical architecture involved, given only the scalp topography, although the high resolution topography provides clear indications of parallel distributed activation across posterior sensory systems and frontal executive systems. This study confirms that controlled working memory processing is associated with early frontal executive activity and related modulation of sensory processing regions.

The initial visual processing of visual word forms and the engagement of frontal attention systems is designed to facilitate the evaluation and integration of attended information in working memory. The results of this study indicate enhanced ERP activity for the working memory task in a posterior temporal N300 ERP. This posterior temporal activity could indicate the early differentiation of visual representations or the transformation of this information into phonological and semantic codes. If this is the case, the activity in this area should be modality specific and larger for linguistic than other stimulus content (see Gevins et al., 1996). The linguistic encoding process may engage inferior temporal cortex and the angular gyrus of the inferior parietal cortex at 300-500 ms (e.g., Nobre et al., 1994; Gevins et al., 1996).

As expected, the clearest indications of working memory activity were large positive potentials over frontal and parietal regions at 400-800 ms. This working memory updating activity is an additional process to stimulus selection and evaluation. The PD550 ERP component clearly indicates that working memory updating engages a fronto-parietal network. The precise sources of this activity are indeterminate from

scalp activity alone, but neuroimaging evidence indicates related neural activity in a distributed, reciprocal associative network, including areas of frontal and parietal cortices (e.g., Goldman-Rakic, 1988; Goldman-Rakic et al., 1993; Posner & Raichle, 1994; Clark et al., 2000, 2001; Moores et al., 2003). The ERP literature has identified stimulus evaluation and working memory processes in large positive potentials at approximately 300-400 ms (e.g., Rösler et al., 1985; Gevins et al., 1996; Chao & Knight, 1998; Nielsen-Bohlman & Knight, 1999). It is well documented that a large positive ERP arises over parietal regions during rare or novel stimulus evaluation (McCarthy & Donchin, 1981; Johnson, 1988). This study identifies similar activity for non-target events, which is not commonly documented in the literature. The P400 and P550 ERPs of this task have similar topography to the conventional oddball P3a and P3b, yet they are elicited by non-target words that required no overt responses. Gevins et al. (1996) identify working memory updating activity in frontal and parietal regions at 300-900 ms. Similarly, this study indicates that both frontal and parietal activity is enhanced during working memory updating. Hence, the ERP findings of these studies are consistent with functional brain imaging studies that report enhanced activity in both frontal and parietal systems, which implicate the frontal regions in executive control processes and the parietal cortex in stimulus processing and retention (e.g., Awh et al., 1996; Dolan et al., 1997; Smith & Jonides, 1999; Prabhakaran et al., 2000).

An important difference between this study and that of Gevins et al. (1996) and Rösler et al. (1985) is the absence of motor responses for non-target events. The non-target stimuli of this study required no overt response, so if the ERP activity observed could be related to any response processes, it can only be the preparation and inhibition of responses to the stimuli once identified as non-target events (cf. Rösler et al., 1985). Rather, it is most likely that these scalp components are related to stimulus evaluation and working memory updating processes, as demonstrated by Rösler et al. (1985).

In theory, fast target detection might be achieved when the target information is represented and remembered as a primary visual experience. This might allow more immediate, visual template matching of the current stimulus event. Often this type of processing is required in the control conditions of the delay match to sample studies (e.g., Ruchin et al., 1990, 1995). This strategy could be implemented in working memory, including activation of the visuo-spatial scratchpad (Baddeley, 1992). If this were the case, the source activity of the visuo-spatial scratchpad may involve visual perceptual functions instantiated in the occipital, temporal and parietal lobes. In this study, the topography of working memory updating implicates parietal and frontal regions, rather than the visual processing regions alone. Thus, the findings suggest that working memory processing has involved not only visual activity but also frontal executive processing.

It is important to consider the encoding of linguistic stimuli in this study. It is possible that visual words are transformed into phonological and perhaps semantic associative representations. Extensive research on working memory processes clearly demonstrates an internal, controlled phonological rehearsal (the phonological loop; Baddeley, 1992). This study presented linguistic information that can be phonologically encoded. Neuroimaging studies of phonological processing indicate left frontal activation, in Broca's area, and some studies implicate the left inferior parietal cortex (BA40) in phonological storage (see Awh et al., 1996; Dolan et al., 1997; Smith & Jonides, 1999; Clark et al., 2000). If there were any indications of phonological encoding, it might correspond with the frontal activity in the later components of this study, such as the P400 and P550 ERPs and the P350 and P500 SCD. However, these scalp components do not clearly demonstrate focal activity over left frontal areas. Previous ERP work has identified phonological processing in delay match to sample tasks (Ruchin et al., 1990, 1992, 1994). In those studies, the left frontal ERP activity

during the delay intervals is clear. In this study, stimulus information may be retained from anywhere between 1.6 to 8 sec, with intervening stimuli during the retention interval. If there is phonological processing in the frontal areas during this study, it is not very clear from the ERP activity for individual stimuli. It may be possible to ascribe some of the parietal activity in this study to the storage of phonological information, but most of the parietal activity did not clearly demonstrate left hemisphere dominance, which would be a clearer indication of such processing. Only the later PD550 ERP/SCD clearly indicated greater left parietal activity. This might be an indication of engagement of this area in transformation of visual to phonological storage, but this study cannot clearly demonstrate the nature of information encoding. Rather, such inferences have been made more clearly during delay match to sample studies, which demonstrate frontal and parietal slow waves that are related to retention of stimulus information in working memory, with different scalp topographic patterns for various stimulus modalities and encoding strategies (Ruchin et al., 1990, 1992, 1994, 1995).

5.5.3 Working Memory Updating in PTSD

There were clear indications of deficits in working memory activity for PTSD patients. A PET study, associated with this report, identified deficits in fronto-parietal networks in PTSD (Shaw et al., 2002; Clark et al., 2003). Similarly, our previous work has identified abnormal frontal slow wave activity during working memory processing (Galletly et al., 2001). Thus, we provide further evidence here of the temporal dynamics of this working memory abnormality in PTSD.

The working memory deficits observed in PTSD are similar to those reported for frontal lobe lesions (e.g., Chao & Knight, 1998; Nielsen-Bohlman & Knight, 1999). For example, Chao and Knight (1998) demonstrate that lesions of the human dorsolateral prefrontal cortex are related to excess thalamic and primary sensory cortex activity, resulting from decreased inhibitory control over these areas. The frontal cortex

is engaged in both modulation of early sensory processing and the later maintenance of absent sensory information in working memory. Chao and Knight (1998) also demonstrate that prefrontal lesions were associated with deficits in a frontal negative potential, indicating impaired processing of relevant stimulus information, suggesting that prefrontal activity is normally involved in facilitating sustained attention for relevant sensory processing. Similarly, Nielsen-Bohlman and Knight (1999) demonstrate that lesions of the human dorsolateral prefrontal cortex are related to decreased novelty P3a activity during a visual working memory task (see also Halgren & Marinkovic, 1995). These findings may be compared with the neuropsychology theory of Kolb (1987), which hypothesized that PTSD patients are susceptible to excessive sensory activation that overwhelms controlled cognition (see also Neylan et al., 1999). It may be that patients attempt to adopt a sensory memory strategy to perform the tasks of this study, as an adaptation to deficient central executive processes. The networks engaged by sensory memory strategies are quite different from the distributed networks involved in working memory processing, which include parietal and frontal cortex (e.g., Cornette et al., 2001). A sensory memory strategy may form part of a complex adaptation to the early detection of threat cues. A sensory/perceptual system primed for the detection of stimulus attributes associated with threat, such as sudden movements, bright colors, load sounds, etc., would provide early detection and orientation to these stimuli. On the other hand, a working memory strategy requires more controlled and discriminating cognitive processes that are more accurate, but at the cost of slower orientation to significance. If this is so, anxiety patients should be quicker to respond to significant stimuli than normal. Indeed, this is the case for threatening stimuli, even when these stimuli occur within a neutral context or where a neutral stimulus in a neutral context has been associated with a threatening meaning (Mathews et al., 1997; see also Attias et al., 1996). When confronted with threatening

stimuli, patients demonstrate greater cognitive responses than normal. Their cognitive system is orientated toward threatening or novel stimuli (e.g., Kimble et al., 2000). On the other hand, the results of our work demonstrate a deficit for processing neutral information in PTSD (McFarlane et al., 1993; Metzger et al., 1997; Galletly et al., 2001; see also Felmingham et al., 2002). Perhaps the strategies and processes required for detection and orientation toward threatening stimuli are not appropriate for dealing with neutral information. Under most neutral stimulus conditions, more controlled and discriminating processing strategies could be more appropriate. Patients may have lost, to some degree, the cognitive flexibility to switch from a highly aroused, sensory processing strategy to a more controlled, working memory strategy and vice versa.

The performance of PTSD patients also indicates deficits of executive functioning. Patients were slower than controls in the fixed target task, indicating a difficulty with target detection processes. That is, patients were able to remember and identify target properties, but they took longer than normal to do so. However, PTSD patients are both slower and less accurate than controls in responding to the variable target task. This suggests particular difficulty with the working memory load of this task. The simplicity of the fixed target task does not elicit poor task performance, as a small decrease in response time could simply reflect a tendency toward greater response accuracy. However, a speed/accuracy trade off cannot account for poor performance of the variable target task. Rather, difficulty in this task is most likely due to a disorder of working memory updating. PTSD patients may be confused about the properties of the target rather than simply taking longer to identify and respond to a target.

A possible alternative interpretation relies on a general bias in PTSD toward false positive identification of significance (Mathews et al., 1997). Patients are sensitive to threatening cues in their sensory array. Ambiguous aspects of the environment that resemble threatening situations are better identified as such rather than suffer the

consequences of having missed a significantly threatening situation (Mathews et al., 1997). This sensitivity to significant stimuli may generalize from threatening cues to a style of processing any significant stimuli. The task materials of this study do not resemble or signify threat, yet patients have a greater tendency toward false positive responses than normal. However, this interpretation would also lead to an expectation of quicker response times to significant stimuli, but this is not the case; patients are both slower and less accurate than controls. Rather, their task performance is indicative of abnormal executive functioning.

It is also important to consider deficits of episodic memory in PTSD, indicated by findings of abnormal personal recollection for neutral events (McNally et al., 1994, 1995) and neuropsychology and neuroimaging reports of abnormal memory functions and hippocampal atrophy (Bremner et al., 1993, 1995, 1997; Gurvitis et al., 1996; Stein et al., 1997; see also McEwen, 1999). The interaction of frontal executive systems with limbic systems is important for integrating current sensory experience with similar episodic memories and associated learning, to facilitate evaluation of potential action outcomes (Halgren & Marinkovic, 1995; Rolls, 1995; LeDoux, 1990, 1995; Nobre et al., 1999; Dolan, 2000; Elliot et al., 2000). A general deficit in this process can impair accurate decision making about adaptive actions. If these executive deficits in PTSD play a role in the relatively simple tasks of this study, it is likely they are more important in complex circumstances, especially involving novelty (see also Kimble et al., 2000).

In this regard, it is interesting to note that controls appear to have a closer temporal conjunction of the parietal P350 ERP followed by the P500 ERP than PTSD patients, suggesting more coherent or efficient processing to evaluate stimulus information and update working memory. There appears to be a greater delineation, even a pause, between these two processes in PTSD patients. This pattern of

component processing may be an indication of greater separation of stimulus evaluation from working memory integration in PTSD patients, which could be an adaptive cognitive strategy designed to implement avoidance of traumatic cognitions. That is, the patients may have developed a cognitive adaptation to traumatic intrusions that involves delayed evaluation of stimulus information and some degree of dissociation of working memory integration from this evaluation process. This could provide an effective means of avoiding potentially traumatic associative encoding for threatening or traumatic stimulus information. The consequence of this process would be greater executive control of these component processes, which requires effortful controlled processing, without being able to make an easy transition to automated learned processing. An important element in this cognitive adaptation is the control over information entering or triggering the episodic memory processes of hippocampal networks (see Nadel & Jacobs, 1996, 1998; Nadel & Moscovitch, 1998). If the executive systems that regulate attention and working memory are effectively dissociating stimulus information from the hippocampal episodic memory system, as a mechanism of avoidance, the consequences are impaired integration of current and previous experiences, leading to an interruption of adaptive action patterns. This processing strategy may apply to all stimulus information, effectively slowing cognition and demanding more cognitive resources. The hypervigilance for threat and trauma cues demands greater executive control over cognition and limits the free allocation of attention and working memory resources to processing stimulus information. The patients may not be able to operate in normal modes of automated cognitive processing, which conserve cognitive resources. When confronted with trauma information, the executive control processes, which are already in a state of greater resource allocation than usual, may be further engaged in avoidance processes and possibly overwhelmed

by the strength of associative processing so that consequent intrusive cognitions dominate awareness.

5.5.4 Conclusions

There was early visual modulation, indicated by the posterior temporal P90 ERP, occipital N150 ERP and frontal P150 ERP, which indicate the early engagement of attention processes in a distributed neural network, involving links between early sensory areas and the frontal executive systems. These effects were found in addition to those already identified due to selective attention for color alone, so the additional demands of the working memory processing may have required greater attention for even early processing stages. There were no clear abnormalities of these early processing stages in PTSD patients.

As in the previous chapter, larger scalp potentials differentiated stimulus conditions after 200 ms, with enhanced ERP activity for the working memory task in a posterior temporal N300, a superior frontal P400 and a superior parietal P550. These effects indicate activity in a distributed network during the updating of visual working memory. The posterior temporal activity indicates the early differentiation of visual representations or the transformation of this information into phonological codes. The following frontal activity may be related to the acquisition and evaluation of information in working memory, while the later parietal activity indicates sustained attention to the information. It is likely that these scalp potentials reflect cortical nodes of a distributed processing network engaged in reciprocal interactions that facilitate efficient information processing and adaptive behavior.

This study has demonstrated deficits for PTSD patients in the frontal and parietal systems during working memory updating. Firstly, the superior frontal P400 ERP was delayed in PTSD patients, which indicates less efficient integration of new information into working memory. This effect was coupled with a smaller parietal P550 ERP in

PTSD, which indicates a deficit in the sustained attention and retention of the new information in working memory. These effects in the P400 and the P550 ERPs were clearly indicated in the PD550 difference wave component, which was smaller in PTSD patients over both the superior prefrontal and the left superior parietal regions. It is possible that a lack of coherent, integrated activity of the frontal and parietal executive systems can explain the failure of PTSD patients to process neutral information efficiently. Abnormal activity in left frontal and parietal areas has been observed in our associated PET study of PTSD (Shaw et al., 2002; Clark et al., 2003). Thus, the present work provides insight into the temporal dynamics of abnormal working memory in PTSD. These findings indicate difficulty with integrating new information into working memory.