Proprioceptive Information Processing in Schizophrenia

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This review has been accepted as a doctoral dissertation together with seven previously published papers by the University of Copenhagen the 21th of September 2010 and it was defended on the 14th of January 2011.

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THE SEVEN ORIGINAL PAPERS ARE:

[I] Proprioceptive evoked potentials in man: cerebral responses to changing weight loads on the hand. S. Arnfred, A.C. Chen, D. Eder, B. Glenthoj and R. Hemmingsen. Neuroscience Letters Volume 288 (2000) page 111-114.
[II] Proprioceptive event related potentials: gating and task effects. S. Arnfred. Clinical Neurophysiology Volume 116 (2005) page 849-860.
[III] Delayed early proprioceptive information processing in schizophrenia. S. Arnfred, R. Hemmingsen and J. Parnas. British Journal of Psychiatry Volume 189 (2006) page 558-559.
[IV] Parallel Factor Analysis as an exploratory tool for wavelet transformed event-related EEG. M. Mørup, L.K. Hansen, C.S. Herrmann, J. Parnas and S.M. Arnfred. Neuroimage Volume 29 (2006) page 938-947.
[V] Proprioceptive evoked gamma oscillations. S. Arnfred, L.K. Hansen, J. Parnas and M. Mørup. Brain Research Volume 1147 (2007) page 167-174.
[VI] Regularity Increases Middle-latency Evoked and Late Induced Beta Brain Response Following Proprioceptive Stimulation. S. Arnfred, L.K. Hansen, J. Parnas and M. Mørup. Brain Research Volume 1218 (2008) page 114-31.
[VII] Attenuation of beta and gamma oscillations in schizophrenia spectrum patients following hand posture perturbation. S. Arnfred, Morten Mørup, J. Thalbitzer, L. Jansson, and J. Parnas. Psychiatry Research, volume 185 (1-2) (2011) page 215-24.

Article IV has formed part of the PhD-thesis "Decomposition Methods for Unsupervised Learning" by Morten Mørup. He aquired his PhD-degree at the Danish Technical University 2008.

Data collection for article II and III concurred with data collection that was reported in my PhD-thesis "Somatosensory Gating in Schizophrenia", University of Copenhagen 2003, and later in articles derived from the PhD-thesis. This means that the subjects investigated in II and III also formed part of the subject samples in the articles [2, 3]. The results of the proprioceptive stimulation have not been enclosed in any previously submitted work with the intention of acquiring an academic degree.

None of the other articles (I, V-VII), or results herein, have previously been submitted with the intention of acquiring an academic degree.

INTRODUCTION
When I interviewed young schizophrenic patients they frequently made me wonder about their symptoms. Some had strange bodily experiences like "water is pouring out of my knee", "somebody is kicking my behind while I sit and watch TV" or "a feeling like my head is pushed into the cupboard" What could be the brain substance of these sensations?

These questions spurred my interest into psychopathology and information processing – what are the elementary processes in the brain transforming input from the body into conscious experience?

In the field of psychopathology I was inspired by Sando Rado (1890-1972), who aimed at describing the essence of schizophrenic psychopathology, and in so doing moved away from the focus on delusions and hallucinations, while centering on more trait-like experiential characteristics.

Rado in [4] described the essence or in his word "the psychologically un-reducible deficiencies" in schizophrenia to be a combination of a proprioceptive disorder, which he considered basic to malfunction in "the circular response pattern of self-awareness and willed action" and a weakness in the ability to integrate pleasure. Puzzled by the patient's somatosensory experiences, I pursued the investigation of the former of these "un-reducible" deficiencies.

MAIN HYPOTHESIS
Rado's hypothesis of a proprioceptive disorder was formulated quite vaguely and considering the ubiquity of proprioceptive information processing in the awake and moving subject, it is also very general. Proprioceptive information integrated with input from the external senses continuously maintains the conscious experience of the body in space. Proprioceptive information processing during movements is important for error correction

and it is an integrated part of the sensorimotor loop [5]. Detection of change of force or dislocation is the passive counterpart, sometimes initiating a remediation, reflex-wise or through voluntary action. The latter process seemed the least complicated of the three to disentangle.

The finding of deficiency in weight discrimination in the schizophrenic patients [6] supported Rado's hypothesis, but it is unclear whether the results emerged as a result of a malfunction at a specific stage of information processing or if it was a result of general imprecision in neural transmission, dysfunction of attention or some entirely unknown mechanism.

Accordingly, the aim of the present series of experiments was to test a narrow re-formulation of Rado's hypothesis:

The brain processing of a perturbation in a stable hand posture is abnormal in schizophrenia

A large majority of investigations of somatosensory information processing use electric mixed nerve stimulation. However it is noteworthy that fast conducting skin afferents seem to be the major type of afferents accessed by electrically evoked brain activity [7-10] and proprioceptive afferents are rarely examined. Likewise, somatosensory processing in schizophrenia has also mostly been investigated through recordings of electrically induced somatosensory evoked potentials. The previous findings in this field and my own results with this method are described in my PhD-thesis. Briefly, my findings could not support the quite established "gating" theory, neither in the somatosensory nor the auditory modality. In the third chapter I describe the above briefly mentioned research in more detail.

1. OUTLINE

The first decision concerned the basic method for an investigation of information processing. If the impact of the brain malfunction is felt particularly in the experience of a percept or an action as suggested by the information processing models [11-17] and if imprecision might is a cardinal feature as suggested by the dysconnectivity theory [18- 19], it is pertinent to investigate brain function in an event related manner having the necessary temporal resolution to follow the timing and intensity of activity in the time scale from stimulus on-set to conscious experience. Brain potential changes happens instantaneous, making event related electroencephalography (EEG) a reliable measure of the temporal signature of an event 20. Furthermore, the logistics of recording EEG are considerable more simple than the imaging techniques, making it an obvious starting point. The disadvantage is the low spatial resolution, making discrete localization of activity rather hypothetical.

The next problem was to find a relevant stimulus and experimental paradigm that could differentiate between the different models for pathology. Some mechanical devices for passive movement had previously been reported, and a few devices for change of torch, but not devices suitable for recordings of event related potentials. The precision of onset had to be in the millisecond range, and the duration of force increase had to be brief 20.

Consequently, the construction of a new proprioceptive load stimulus, the design of a new type of stimulus paradigm and lastly the encouragement of new ways for data analyses were necessary developments. Investigating these new methodological elements in healthy volunteers were necessary steps on the route to test the main hypothesis. The results of these studies are reviewed in chapter six: Methodological developments, while the results of the experiments in patient groups follow in chapter seven: Main findings and discussion of the clinical studies.

Prior to this, in chapter four, the basics of EEG and event related EEG data processing is briefly covered for the benefit of the reader unfamiliar with brain electrophysiology. This is followed by a brief overview of the series of experiments in chapter five.

Forthcoming, in chapter three, are brief reviews of investigations of proprioception in general, of proprioception in schizophrenia and of models of information processing.

2. BACKGROUND

Proprioception

Proprioception has been defined as encompassing four kinds of sensations: 1) Sensation of passive movement. 2) Sensation of active movements = kinaesthesia.3) Appreciation of position in space and 4) Appreciation of force applied 5. The sensations are based on somatosensory information but not all types of somatosensory input are involved. Cutaneous, joint, tendon and muscle stretch afferents contribute to proprioceptive sensations 5, [21-25], while temperature sensors and some of the superficial skin sensors do not contribute. Discrete tactile sensations are distinct from proprioception as they, like vision and audition, are part of the external senses. Deep pressure sensors in the skin contribute to the sensation of proprioception as they are activated by displacement and distension due to muscular contraction [26]. Apart from the main somatosensory afferents, that ascend in the dorsal volley and terminate in the primary somatosensory cortices, muscle afferents have a direct pathway to motor cortex [27, 28]. These feedback afferents probably form the afferent loop of a cortical response called the long latency stretch reflex [29-33].

Computational models of voluntary movements include elements of feed-forward trajectories of the wanted movement and elements of kinesthetic feed-back and error correction pending on the successfulness of the movement. The regions involved, observed in imaging studies, are the primary somatosensory cortex, supplementary motor area and inferior parietal lobule. When proprioception is in the focus of attention, additional activation is seen also in primary motor cortex, associative somatosensory area and the posterior insula [34-37].

Proprioception has been investigated by many ingenious setups: mechanical passive limb displacement [22, 38, 39], vibration [40-43], blindfolded or anesthetized position or weight matching [44-49], and positioning of loads or instruments modulating force or perturbation movements [9, 32, 33, 50-58]. Only a few of these methods were created with the aim of recording brain potentials [33, 39, 50]. Mima and colleagues produced a fast passive flexion of the right middle finger, while Goodin and colleagues recorded a perturbation introduced in a ballistic movement of the arm. Alary and colleagues used an assistant to make a brisk passive finger extension.

Previous studies of proprioception in schizophrenia

A few reports of proprioception in schizophrenia exist. Older studies have mainly investigated weight discrimination and the ability to sense the directions and length of passive movements [6, 59] Only the former ie discrimination of small weight differences to a load of 40g yielded significant differences between schizophrenic patients and healthy comparison subjects[6]. A replication of the results failed [60], but a more recent study aimed at investigating transient memory storage confirmed a weight discrimination deficiency in the patients [61]. Interestingly, a new study shows that weight discrimination is also deficient in relatives to schizophrenic patients compared to relatives of bipolar patients and healthy subjects [62]. Error correction during a tracking movement of the hand, when the patients have no visual feed-back, is compromised [63]. A special case of tracking movement – eye-tracking of visual objects – are deficient in schizophrenic patients, but this has been considered more to be an error in the trajectory planning than an error in the eye muscle feed-back [64].

Studies of motor activation has shown decreased left parietal activity in schizophrenia when using EEG [65] and decreased activity of somatosensory cortex when using functional imaging [66].

Studies of electrical stimulation of mixed nerves and the somatosensory evoked potential in schizophrenia are much more abundant, see review in [3], but they do not contribute to the understanding of proprioception as it is mainly tactile exteroceptive afferents that are assessed, and because none of the complex sensations defined as proprioceptive are evoked by electrical stimulation.

In conclusion, the research on proprioception in schizophrenia is sparse and the investigations have mostly been aimed at proprioceptive discrimination ability. Considering the decline in attention capacity observed in at least a third of the patients [15], rigorous control for this has to be part of the experimental set-up. Even more important is the fact, that it is the outcome of proprioceptive information processing that has been assessed, not the processing in itself. Several relevant theories have been advanced concerning the possibility that the schizophrenic deficiency pertains to a specific function of the brain processes leading to conscious sensory experience.

Information processing models in schizophrenia

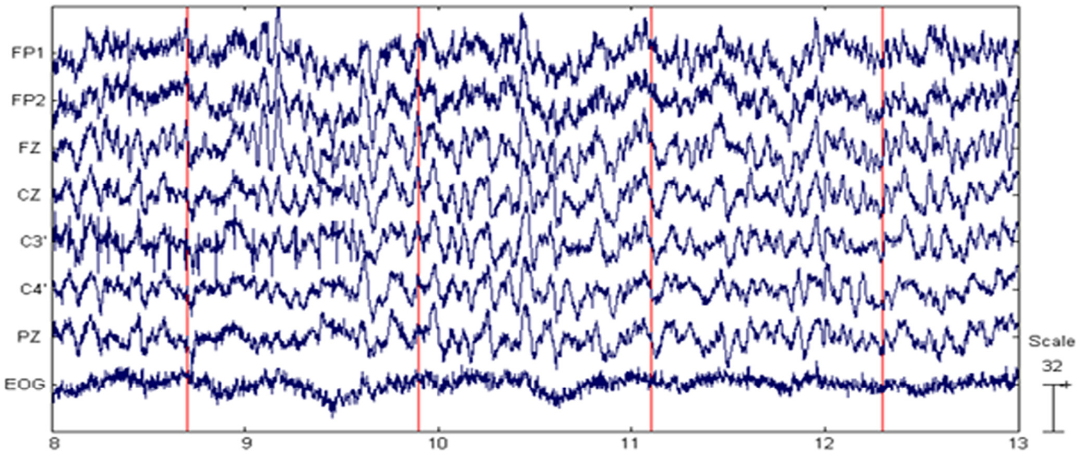
When it comes to other modalities of sensory processing, we know more of the processes involved. Within the last decades auditory and visual information processing has been a major area of interest in schizophrenia research. Diminished attention capacity is a very reliable but also a very general finding as exemplified by the findings of a consistently attenuated event related potential P300 amplitude [67]. Looking for more specific findings and for more specific models for the deficits in information processing, three models are well-described and supported by empirical findings.

The early findings of a specific modulation of reaction time depending on the regularity of stimulus presentation [68], led to a theory of a deficiency of the ability to maintain the context of the stimulus in working memory. This means that for the schizophrenic patient the response to a new stimulus resembles the healthy response to a well-known stimulus, while the response to a well-known stimulus resembles the healthy response to a new stimulus. This seemed to indicate that the patients were unable to profit from the effect of regularity or other relevant context. Elaborating on the theory, Hemsley suggested that the emergence of a relevant response bias is deficient in the patients [11, 69]. The response bias is suggested to be dependent on memory function and on a comparator function probably located in hippocampus. The memory function is, of course, for retrieval of the preceding events, and the comparator function is for the evaluation of resemblance of the present stimulus to the previous events. It is quite difficult to separate the effects of memory function and comparator. Mostly it has been done by assessing the effect of increasing the stimulus intervals, considering the comparator to be intact if the long intervals produce relatively more abnormal responses in the patients [70]. This makes an impaired precision in the hippocampal comparator a possible candidate for a specific stimulus processing deficiency, as also suggested by several other types of clinical studies and substantiated by pre-clinical models [12].

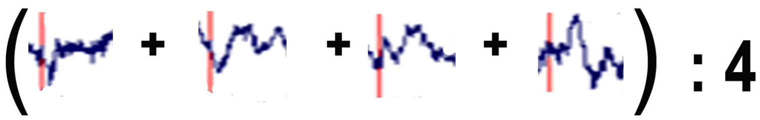
Looking at even earlier processing relative to stimulus presentation, the inhibition of the response elicited by the second stimulus of a pair is the main point of another hypothesis. Gating of the auditory event related potential P50 and pre-pulse inhibition of the startle reflex are two measures that track the ability to inhibit a response to a sudden stimulus, when it has been preceded shortly (500 ms) before by either a less intense stimulus (pre-pulse inhibition) or by an identical (P50 gating) stimulus. Several studies, but not all, have shown that P50 gating is deficient in schizophrenia [71-77]. A filtering process is suggested to protect the cortical regions from sensory overload, which would result if both stimuli of the pair elicited equal responses. The theory posits that sensory overload results in psychotic symptoms [72, 78], although a correlation to psychotic symptoms has been difficult to establish [77, 79]. In a sense the “gating” hypothesis could be seen as a specification of the hypothesis of a deficient comparator function as the stimulus would need to be assessed for resemblance before the response is inhibited. Yet, this is not the way it is conceptualized [80].

The last of the presented models is more centred on the action or response part of the stimulus-response circle. Feinberg and Frith suggested, that thoughts and actions without any motor component follow the same elementary processes as voluntary movements [13, 14, 81]. Applying this, Frith suggested that when thought or action is initiated, two down-stream routes are accessed, the first is the content loop of cortical activation – which could be the motor cortex in case of a verbal utterance -, the second is a feed-forward representation, in this case, of the phrased words to the auditory cortex [17, 82]. This second loop has also been named the corollary discharge loop. The idea is, that the feed-forward representation introduces a pattern in the auditory cortex, which could be matched to the incoming sound of own voice, in this instance serving as the feed-back. Of course the feed-forward volley also arrive in the sensory cortex at the same time representing the activation of throat, tongue and facial muscles involved in verbalizing. The feed-back to the sensory cortex would consist of proprioceptive input from muscle afferents and tactile sensors, the latter firing due to skin/mucous membrane displacements. Frith suggested that it is the smooth match between the feed-forward representation and the feed-back, which induces the feeling of agency. Agency is the subjective knowledge that I am doing the talking in opposition to the feeling that somebody else is talking using my voice [17]. Lack of agency could be the substrate of the delusional symptoms of influence and alien control frequently encountered in schizophrenia [17, 82].

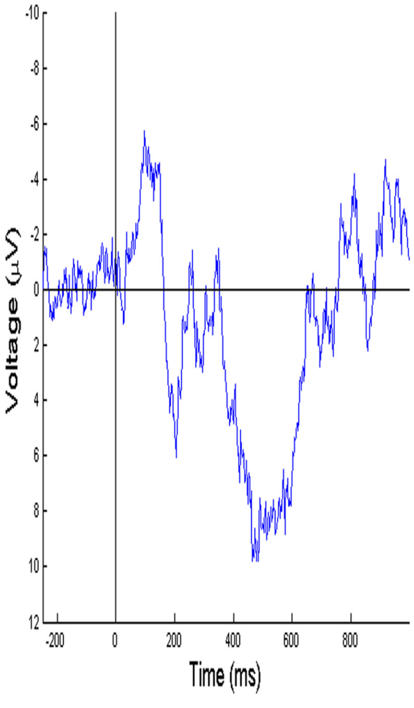
In their original formulation, the filter deficiency and the comparator imprecision is the most distal of these three models, i.e. close to the sensory input volley, while the corollary discharge deficiency is closer to the output response. But even the corollary discharge model seems to include elements of comparison and context updating; in this case, between the feed-forward model which entail the specific context of the action, and the feed-back input..



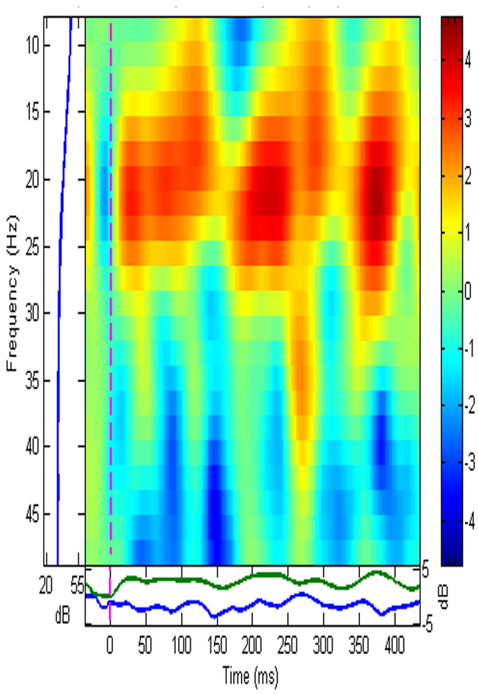
Continous multi-channel EEG ; four events marked



Epochs in one channel are averaged



Averaged amplitude time series:
Event Related Potential - waveforms



Averaged time-frequency power series:
Event Related Oscillations - TF-maps

Figure 1

Event related EEG averaging.

For EPs or ERPs the continuous EEG recording is cut into pieces determined by a time range relative to the stimulus onset (top row, stimuli marked by red vertical lines, recordings from 8 electrodes). Then the resulting epochs are averaged separately for each electrode (second row). If this averaging is performed in the time series domain the result is a waveform (bottom row, left) which is described by its peaks. The peaks are identified by there polarity, amplitude and latency, see figure 2. More recent techniques make use of time-frequency transformations where the event related activity is extracted for each frequency bin. In this way the activity is described by frequency, time and intensity (the colour-bar represent power or voltage) in a time-frequency plot (bottom row, right).

The mentioned information processing models are a-theoretical in relation to the origin of the deficiencies, but basically they are all well-adjusted to the theory that schizophrenia is a neuro-developmental disorder [83, 84]. This, quite established, hypothesis states that the illness is a manifestation of biological determined processes based on genotype or negative environmental exposure in the womb or early infancy [83, 84]. The course of the illness could be seen as a result of the modulation of the illness processes by age related phenomena i.e. onset of illness in adolescence and menopause due to hormonal changes and social adjustment [83, 84]. Again the specific nature of the biological processes hypothesized to make the subject vulnerable to schizophrenic diathesis is an important research question, particularly engaging genetic investigations [76].

Based on the antipsychotic effect of dopamine receptor blocking medication the dopamine neurotransmitter system has been scrutinized for possible candidates for neuro-developmental aberrance [85]. It seems that the dysfunction of the dopamine loops is an endpoint of more basic disturbances [86]. Several other brain neurotransmitter systems have been implicated [19, 86], but an exposition of the possible transmitter deficiencies in schizophrenia is outside the scope of this dissertation.

Another type of wide-spread affection like a general aberrance of cortical connectivity has also been suggested [19, 87]. It could be the result of faulty generation and degeneration of synapses or lower density of white matter cells. The dys-connection theory is supported by the post-mortem finding of reduced neuropil in the cortex of schizophrenic subjects [19, 88-90]. The decrease in connectivity could lead to a condition of abnormal or imprecise cross-regional interaction of cortical neurons [19, 91].

It seems possible to apply any of the information processing models to processing of proprioceptive information, but the distal models would seem the most efficient to disentangle the sensory-motor loop and to define a weakness as affecting proprioception proper without involving movement execution. Of course the caveat would be that the distal models mostly have been supported by experiments with visual and auditory stimuli, while the corollary discharge model is examined in set-ups with voluntary movements.

Event related EEG

Surface EEG measures the momentary potential field existing over the scalp. The scalp potential field depends on the sum of current sources and on the volume conduction properties of the head [92]. As cortex is closest to the recording electrodes and the cortical neurons and projections are arranged in an orderly fashion, the scalp potential is mostly derived from cortical activity [92, 93]. Of course, it is essential that it is the brain activity that is measured. Surround electric noise is a one serious problem when doing EEG recordings and another is the subject related artifacts like movements or blinking. The end result depends heavily on the recording technique and data processing [94].

When examining information processing, the EEG recording is combined with an experimental paradigm including one or more type of stimulus and frequently a task to be solved by the subject. The electrodes are placed according to a convention, mostly the international [10-20] system and its later extensions. The data then consists of the channels for the EEG measurement, electro-oculogram (EOG) channels for artifact detection, an event channel for the registration of the timing of the stimuli and lastly possible channels for accessory measurements like electromyography (EMG) or heartbeat. After recording, the EEG data is cut into pieces in a fixed latency window around the time-point of the stimulus onset. These pieces are called epochs or single-trial potentials.

Specific elaborations of the measures described below exist, and the research field is cluttered with acronyms. To avoid confusion only the measures later applied are described in detail.

For traditional evoked potentials (EP) or event related potentials (ERPs) the EEG epochs are averaged, i.e. the amplitude at each identical time-point is summed and subsequently the sum is divided by the number of epochs. In this manner, the random activity of the brain and external or internal noise that is not event related is levelled out, while the event related activity is amplified. The resulting waveforms are described by its peaks, which are identified by their polarity, amplitude and latency. See figure 1, left side. P300 is a well-known cognitive component seen in the event related potential of a target stimulus demanding a response either overt as a button press or as silent counting [95, 96]. It is named P300 as it is a positive voltage waveform peaking approximately 300 ms after stimulus. It is traditionally recorded in an odd-ball paradigm were the target stimuli are interspersed among frequently presented standard stimuli which do not require a response. P300 has in detail been characterised by the modulation of latency and amplitude by 1. Stimulus features like intensity or perceptual distinctiveness of the target compared to the standard stimulus; 2. Paradigm features like temporal probability and attention direction and 3. Subject variables like attention allocation, motivation, IQ and personality [95, 96]. See figure 2 for an illustration of ERP components. While the P300 paradigm tracks the effect of attention on later event related potential components (< 100 ms) other paradigms are employed to assess the early pre-attentive activity.

The early cortical EP components decrease in amplitude if they are presented shortly (< 8 s) after one another [97]. The P50 waveform is a middle latency component mostly described in the auditory modality, but it has also been described in the somatosensory modality [98-101]. The effect of repetition, also called gating, is most pronounced from the first to the second stimuli in a row [99-101]. In between the early sensory peaks and the later cognitive components, the process of stimulus recognition, deviance detection and orienting towards the stimulus is tracked by the N120-N140-P200-N260 complex, which has been variously subdivided [102, 103].

Instead of describing the stimulus related EEG activity by the time series averages, as the EP or the ERP, more recent techniques make use of transformation of the data into the frequency domain. In so doing, the single trial analyses are described by frequency and power i.e. a polarity-free measure of amplitude (second degree amplitude) and averaged subsequently. The frequency measure can extracted through wavelet transformation yielding the frequency, power or phase at each time-point. Again this activity has to be measured across many stimuli to extract

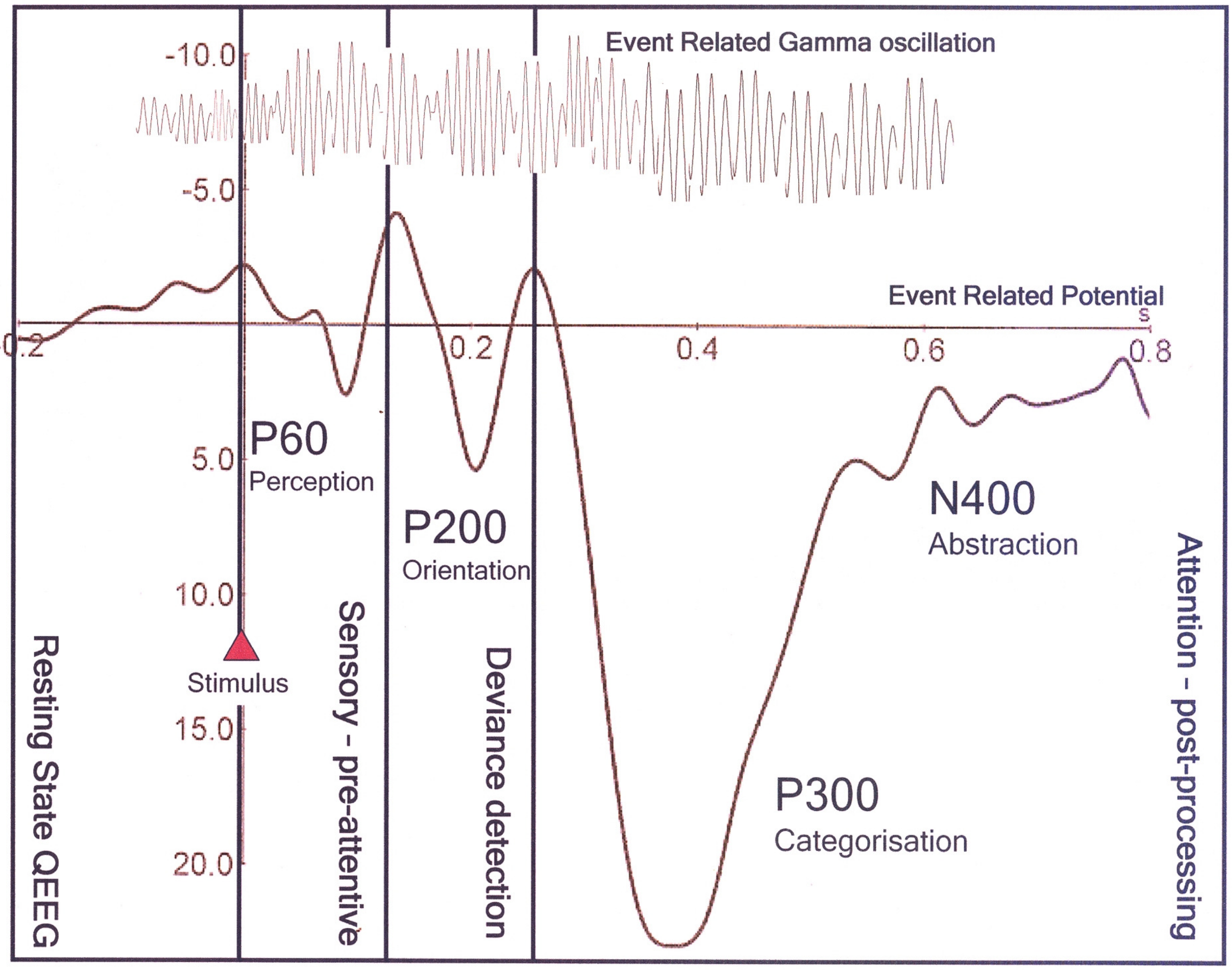


Figure 2 ERP waveform and information processing stages
This is a simplistic overview of the information processing stages related to the ERP. At top the event related gamma activity is inserted. The high frequency activity is rarely represented in the ERP due to the low power and the extreme phase precision necessary for high frequency activity to emerge in a time series average. The cognitive processes are mapped relative to stimulus onset at zero. Negative is up. In the resting state the continuous EEG is quantified by region and frequency distribution (QEEG). In the ERP, the early sensory evoked activity P50-P100 (depending on sensory modality) is followed by deviance detection and orienting (N120-P200). Attention to the stimulus and decision about its relevance to the task at hand emerges as a large parietal positive waveform (P300) while later slow waves like N400 or Slow Negative Waves (SNW), frequently maximal in the frontal region, are seen when demands on working memory are increased in semantic or arithmetic tasks. The early gamma activity is related to sensory processing and perception while later gamma activity is attention dependent. This figure is an elaboration and modification of a figure in [1].

relevant activity from the random background activity and noise. See figure 1, right side.

Oscillatory activity is reported in a variety of measures, which are quite dissimilar. Evoked amplitude and power measures can readily be compared but they may have different temporal resolution. Evoked activity is early and it is expected to be phase consistent in relation to the stimulus while induced activity is later and in random phase [104]. While it has been suggested that the two measures are derived from the same source [105], it is not straightforward to compare them as indices of information processing, the induced activity being at a much later stage (> 200ms) than the evoked activity (20-100ms) [106]. A specific stimulus driven method of eliciting gamma activity (activity approximately at 40 Hz) is achieved by a stimulus presentation at the frequency of 40 Hz; it is relevant for testing the capacity of the intra-cortical interneuron networks for producing the high frequency oscillations [107]. Phase consistency measures, can be across epochs (trial-to-trial phase consistency, phase-locking factor or as denominated presently: inter trial phase correlation (ITPC)) as an indication of precision and local synchrony or across electrodes (cross region phase consistency, cross coherence or synchrony) as an indication of long distance coupling. A long standing discussion about the interpretation of the ERP as resulting either from phase resetting of oscillatory activity also present in the ongoing EEG [108], or as a combination of several true polarized single high amplitude bursts seems to have come to a rest at the point where the ERP primarily is seen as depending on phase resetting of oscillatory activity [109, 110]. This has led to an increasing interest in examining the event related EEG activity in time-frequency plots, rather than only looking at the time-series of the event related EEG voltage. Activity in the gamma and beta (15-25 Hz) frequency range is predominately a manifestation of cortical activity while lower frequencies (alpha, theta and delta) are generated in sub-cortical structures [104]. Focal evoked gamma activity is estimated to be due to cortico-cortical networks spanning app 1 cm in diameter, while beta frequencies have been suggested to be the fast media for cross-regional cortico-cortical coherence [111, 112]. The synchronous excitation of cortical neuron assemblies across the brain is suggested to be basic to perception and sensory-motor integration [113, 114]. Gamma cross regional synchrony is assumed to be the vehicle of perceptual binding, i.e. the formation of a single percept from a variety of intra-modal features of the object or event [88, 107, 114, 115].

3. OUTLINE OF EXPERIMENTS

The first experiment investigated the possibility of eliciting an evoked potential by the purpose build stimulus device, made to induce a brisk change of load on a hand held load. Ten healthy males were included. The 80 g stimulus was presented regularly in the right hand. EEG was recorded in 7 scalp electrodes, EMG on the right forearm (I).

The next experiments tested the effect of paradigm manipulation on the evoked potential elicited by this load stimulus. A no-task and a task paradigm were assessed corresponding to previous described paradigms for the measurement of gating and attention (P300). A 100 g stimulus was presented regularly in the no-task paradigm and irregularly in the task paradigm. Twenty-four healthy male subjects, not previously examined, and 12 male patients with schizophrenia were included. EEG was recorded in 7 scalp electrodes, EMG on the right forearm. (II,III)

Further experiments investigated if the load stimulus evoked oscillatory activity, including gamma frequency (30-80Hz) oscillations, and explored the effect of paradigm manipulation on the evoked activities. The 100 g stimulus was applied in both hands in two no-task paradigms each presented three times. Data from a simple one hand paradigm was used for the initial exploration while two hand-alternation paradigms were designed to test the effect of stimulus sequence on the different frequency components. A new multi-way decomposition for time-frequency transformed data was developed and for this purpose a well-described visual task was recorded in 11 healthy men. In the investigation of proprioceptive EPs, 14 other healthy subjects (4 females) were included and EEG was recorded in 64 electrodes. (IV,V,VI)

The last investigation compared the high frequency components evoked by the proprioceptive stimulus in 18 (11 females) schizophrenia spectrum patients and in 18 age- and gender matched healthy comparison subjects, not previously examined, using identical procedures and data-processing as just established in healthy volunteers (VI) although only recording one presentation of each paradigm (VII).

4. METHODOLOGICAL DEVELOPMENTS

The proprioceptive stimulus

Description of the load stimulus equipment

To be able to track the brain processes involved in the sensation of change of force, a device was developed to induce a brisk addition of force to the gravity of a fixed load, simulating a naturally occurring proprioceptive event. A small machine exerted an adjustable downward pull on a wire connected to a handle, see figure 3. Considering the previous findings within schizophrenia, where particularly the small weight changes had been difficult for the patients [6], the range of adjustment was 0-100g. The wire was also loaded with a stationary weight of 400g. In this way the change of gravity could maximally be a 25% increment.

The pull was executed by an electromagnetic spool with high precision and the relationship between the onset of winding and the development of the pull was fast and linear, increasing the load with 20g every 10 ms. The offset of the winding had the same properties. The stimulus delivery was controlled by a unit placed 3 m from the devices. This unit was initially controlled by a DOS-system PC (I, II, III) later by Presentation© software on a Windows based PC (IV, V, VI, VII). Engineer Svend Christoffersen at the Department of Medical Physiology, University of Copenhagen, made the technical design and the programming, and the equipment was build at the engine shop facilities at the University. Two stand alone devices were made, one for each hand. They were easy to move to adjust the position according to the convenient location of the hand. When the stimulus was delivered, the plastic handle was held loosely in the grip of the hand, the handle resting on the middle of the thumb and the distal part of the other digits. The arm rest support extended from the elbow to the root of the hand ending at the level the first articulation of the thumb to avoid bending of the wrist. The arm rest was always horizontal, but the height of it and the angle of the arm were adjusted individually for maximal comfort.

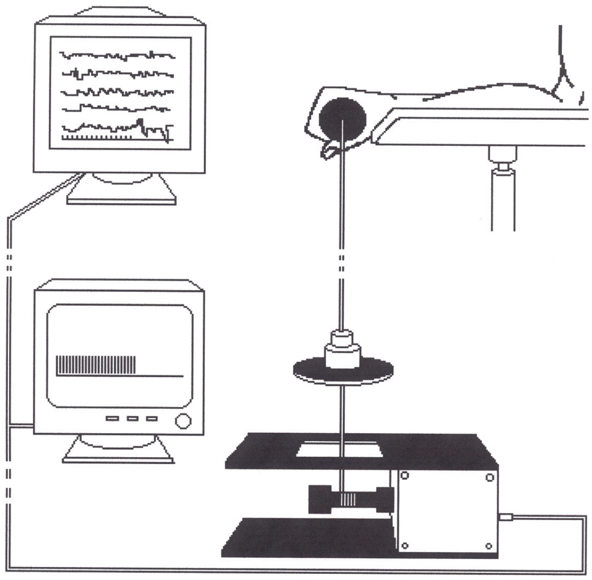


Figure 3. The proprioceptive stimulus
The forearm and hand is supported to the level of the thumb joint. Stimulus was a linear weight increment of 20 g in 10 ms to a maximum total load of 500g.The stimulators were controlled by a PC, which delivered a trigger stimulus for the EEG event channel. The drawing was made by Bo Jacob Hasselbalch, 1999. (I)

Sensation evoked by the load stimulus

Pilot studies showed that the load stimulus was only reliably detected when the load increment was more than 20g. In a brief load discrimination task, including increments of 25, 50 and 100 g, the number of errors varied between 0 to 4 in a total of 12 trials (mean 2.0, std 1.2; N=24) (II). The 100g stimulus was experienced as a brisk and light change of load, resembling a failure of muscle contraction or a pull from below. It was quite variable, how difficult it was to discriminate between the 40 and 100g increment stimuli in the right hand with eyes closed (II). Across six tasks of 40/100g discrimination, where either the 40 g stimulus or the 100 g stimulus had to be counted and the correct number was in the range of 21-27, the total number of errors varied between 1 and 19 (mean 6.9, std 4.6, N=24) (II). The stimulus was not offensive, and it was easy to think of other things, when it was applied without any task (V,VI,VII). Using the mixed set-ups where the load stimulus was applied in some runs while auditory or visual stimuli was applied in intervening runs (II,III, VII), or the runs alternated between one hand and the other (V,VI), muscular fatigue was a rare complaint.

Brain activity evoked by the load stimulus

The early evoked potential elicited by the 80-100g load increment was small i.e. of low voltage (I, II). The time-series average showed a contra-lateral parietal P60-70/ N160/P200 configuration and a frontal N70/P100/N160/P200 configuration (I, II) see figure 4. In the later experiment the configuration was the same although a 10 ms delay in latencies was seen (VI). This was due to the digital low pass filter applied after averaging. A load increment of 40 g elicited a very small potential, which was only recognizable in the grand averages across subjects, while it was unidentifiable in the individual averages (II).

The middle-latency proprioceptive evoked activity could be decomposed into five components in the contra-lateral hemisphere each tracing a specific time-frequency window. Gamma activity (40-80 ms; 29-45Hz) (V, VI, VII) was the first activity that emerged followed by the bifocal frontal-parietal alpha-beta oscillation (50-110 ms; 10-18Hz) (VI). Then the contra-lateral parietal beta activity (80-105 ms; 18-25Hz) evolved, this component had a cross-hemisphere parietal and central frontal distribution (VI,VII) and it was followed by a more central slow lateralized frontal alpha-beta activity (95-130ms; 14-15Hz) (VI). In the end a large amplitude low frequency bifocal parietal-frontal alpha-theta emerged (100-140ms; 7-8Hz) (VII) see figure 5.

The gamma activity observed at the central parietal electrodes in experiment (V) was slightly later and more central than the ITPC maxima observed after the same stimulus in (VI, VII). Differences in wavelet algorithm and normalisation procedure could explain that.

While the initial reports only encompassed right hand stimuli, the later recordings included both hands (V-VII). Left and right hemisphere did not differ in frequency, timing or precision of the evoked oscillations.

Methodological issues related to the load stimulus

The stimulus was conceived to exert an increase of force momentum without any change of hand and wrist position. Due to the lack of hand fixation a small perturbation was inevitable, in this sense possibly also leading to other aspects of proprioceptive sensations like the sensation of passive movement and up-dating of body position in space. The lack of hand fixation was intentional as a totally fixated and supported hand would have changed the input from a force exerted on muscles to a force exerted on subcutaneous soft parts. The perturbation was minimized by the fact that the increment in weight was very slight and by the support of the root of the hand.

The lack of fixation also gave way for individual solutions as to the grip of the handle: some subjects might have involved mostly the grip function, some mostly the biceps muscle to maintain hand position. In the same manner, although the subjects were instructed as to the firmness of wrist position (in (I) it was to be kept stiff, and in the later experiments they were instructed to maintain a relaxed position and allow the natural hand perturbation (II-VII)), the muscular tension was not controlled by on-line EMG. Strict voluntary control of muscle contraction perhaps even with the application of bio-feed back EMG for self monitoring, as frequently applied in studies of motor control, would have shifted focus of attention to the motor control, which was not the intention. The intention was to make it possible to manipulate the level of attention on the stimulus itself depending on the paradigm. Another reason for the lack of control of contraction was the expectation that the patients would have difficulty with complying. While the lack of control of contraction could have imparted high variability of amplitude of the evoked potential, the lack of EMG difference indicated that level of muscle contraction was not the explanation for the subject variance (II, III, VI, VII).

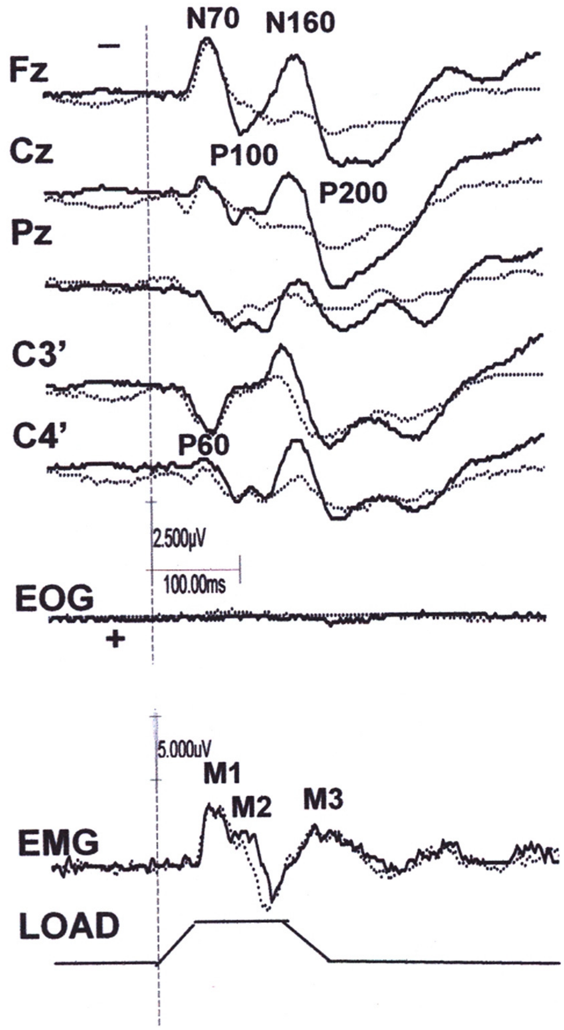


Figure 4. Grand average of the proprioceptive EP
The proprioceptive EP following paired right hand stimuli. Load: 100g. Stimulus 1: solid; Stimulus 2: dotted. N=24. At bottom, the time course of the proprioceptive stimulus is illustrated in arbitrary units (LOAD). Stimulus onset corresponds to y-axis. Frontal central (Fz), vertex (Cz), parietal central (Pz) contra-lateral parietal (C3'), ipsilateral parietal (C4') electroculogram (EOG) and EMG of the forearm extensor muscles (II).

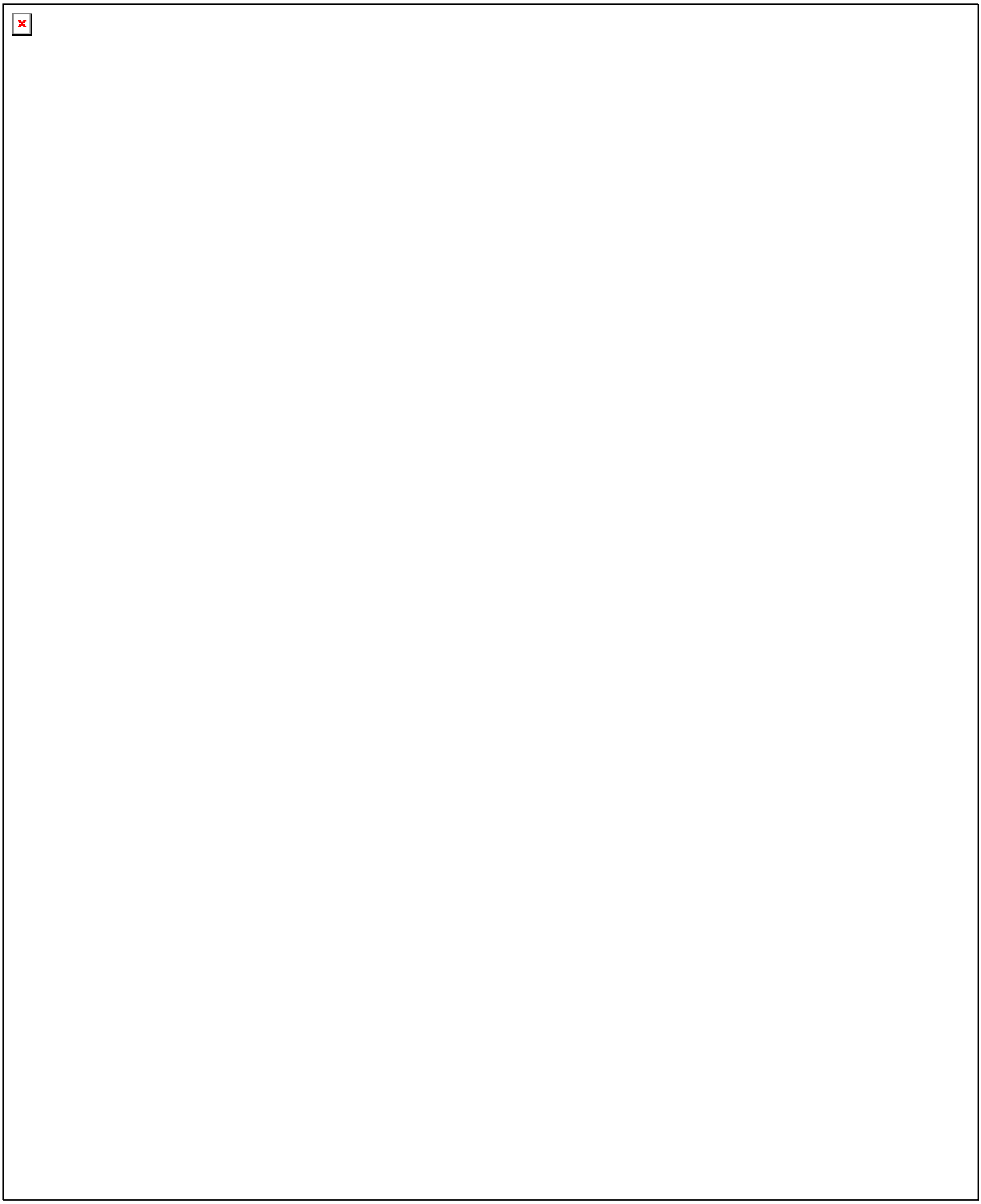


Figure 5 . The proprioceptive EP decomposed
Right hand proprioceptive activity shown at the onset of the 100g load stimulus. The analysis was performed on a grand average of 8856 epochs. N=14. These are the results of the non-negative matrix decomposition, asking for 5 components in a window of interest spanning 0 – 200 ms and 7 -47 Hz and a full head cap of electrodes (64). The decomposition spans two dimensions: channel (head plot) x time-frequency (time-frequency plot). This means that the presented time-frequency plots are a distillate of the time-frequency plot of all channels. The topography at the left shows the major regional focus of the component characterised by the time-frequency signature seen in the time-frequency plot at the right. The components have been arranged to appear in a temporal sequence from top to bottom (VI).

A small humming noise was generated by the apparatus making it necessary to apply background white noise to shield off the sound. A mechanical aspect of the design of the stimulus was not foreseen: The 400 g load mounted on the line tended to go into small circular swinging movements, if the stimuli happened to fast after one another. This gave way to quite interesting deceptive perceptions of wide circular movements of the load. As the swing was generated after the load event it was not assumed to be critical, but to avoid the complication, ISI were always more than 1 second. Regrettably, the tool-like extension of perception to the load itself has not yet been explored.

The temporal evolution of the stimulus was linear. This meant that the maximum of a heavy increment would be achieved at a later time than a lighter increment, i.e. 40 g increment reached the maximum value at 20 ms after stimulus onset, while 100 g increment reached it at 50 ms after stimulus onset. As it became evident that the light increments elicited too small potentials to make it feasible to record the many trials necessary in cognitive paradigms (II, III), the stimuli were merely included as part of the task of discrimination. The potentials were not analyzed. As the first brain activity following the 100 g increment is seen already 60 ms after stimulus onset and the electrical peripheral transmission time is at least 12 ms, it is the advent of the change in force, that elicit a recordable primary activation, which subsequently are intensified as the increase in load involves more sensors. Duration of force is also one of the factors modulating the long-latency response, see below.

Additionally, it was apparent that the off-set of the load also was a force change, which elicited an evoked potential, se figure 6 (VI). This phenomenon of off-set potentials has also been described for auditory stimuli, but it has not extracted much attention 1. When looking at evoked gamma activity it is very important as stimulus off-set might interfere with the phase-locking evoked by the onset. This made the extension of load duration in the later experiments necessary (V-VII). In retrospect, the large N160 peak seen in the first recordings (I, II, and III), see figure 4, could be a combination of a response to stimulus offset and a frontal processing negativity described in this latency range [116].

The way the time-frequency evoked components were extracted, was quite new (IV-VII) and [117], and it is difficult to make comparisons to previous studies, where topography and time-frequency signature is not integrated into one measure. The component pattern is not a fixed solution as it is dependent on the number of components asked for and the time-frequency range included in the analysis. The algorithm gave less weight to topography than usually done in separate analyses of regional difference, hence it was not attempted to investigate details of topography or make backward source localisation of the activity. As such verification of the cortical sources is still lacking, as it is in many ERP studies, where knowledge of the anatomical substrate of the activity has to be achieved through supplementary functional imaging of the same stimulus and paradigm.

Comparison to previous EEG studies of proprioception

As proprioceptive information is part of the feed-back control of voluntary movement, it has been investigated along several lines of research within the programming and execution of voluntary muscle contractions. If only considering the research including cerebral evoked potentials this includes: 1. studies of the movement related potential i.e. the EP before and during movement execution [118-120]; 2. studies of the trans-cortical long-latency stretch reflex, where the cortical activity is related to the EMG response [33, 121-123] and 3. studies of passive movements aimed at a selective mapping of muscle spindle input as a mean of investigating neurological disorders [39, 50, 124, 125]. These passive movement potentials have been named proprioception-related EPs.

The load stimulus was most easily compared to the different types of mechanical stimuli used to elicit the long-latency stretch reflex [33, 121-123], but only a few of studies have used a comparable recording technique and epoch length, which can justify detailed comparison of the brain responses. The latencies of the potential would be expected to be delayed compared to stimuli having a faster rise-time like some tactile devices and electrical stimulation.

The load stimulus initiated an EP waveform at the contra-lateral parietal electrode that in each individual EP looked very much like the earlier recordings of mechanically induced EPs of passive movement [50, 126], muscle magnetic stimulation [127] and muscle stretch [32, 33, 123]. But no double positive waveform was observed in the study of passive finger movements 39. As noted above, stimulus offset might have evoked this double waveform, as it was not re-produced in the later ERPs (VI,VII), please compare figure 4 and figure 13.

As the long-latency response has been considered specifically related to posture [33, 128] it was expected in the load experiment. The load stimulus evoked an EMG activity similar to the long latency response (I, II), even though it was not preceded by an evident early monosynaptic spinal stretch reflex, see figure 4. In a study of the long latency stretch response of the wrist extensor muscle a perturbation was introduced in a ballistic – isotonic - movement [33]. A prominent negative waveform was demonstrated at vertex when the subject had to oppose an unexpected change of force, while it was not seen when it was expected. The negative peak and the long-latency (EMG) response correlated positively.

In a study of passive and active movements, a waveform reversal, similar to the one evoked by the load stimulus, was seen in both active and passive conditions and dipole source analysis supported the view that the feed-back activity was generated by the primary somatosensory cortex or the primary motor cortex [129].

The gamma frequency activity mapped in (V, VI, VII) would only contribute a little to the EP, as the high frequency components have much lower amplitude than those of lower frequencies. No previous recordings of evoked gamma activity following mechanical stimuli have been found.

The evoked activity of the contra-lateral parietal region spans all frequencies, and the activity evolves in an orderly fashion with different spreading patterns for the different frequency bands. Due to the smearing of the temporal resolution induced by the wavelet transformation it is not possible to define the exact timing of the sequence of events. In studies of movements and somatosensory stimulation, involvement of primary somatosensory cortex renders oscillations in the gamma range, while simultaneous involvement of motor and somatosensory cortex renders oscillations particularly in the beta frequency range [130-135]. This distribution of gamma and beta oscillations is in agreement with the topography seen in figure 5 (VI). Evoked beta activity is less explored, but beta oscillations have been observed in the contra-lateral motor cortex during isometric hand muscle contraction [136, 137] and beta activity is suggested to promote sensory motor integration [135]. This is in accordance with the fact that the proprioceptive stimulus necessitates isometric muscle contraction for a stable hand posture and continuous sensory-

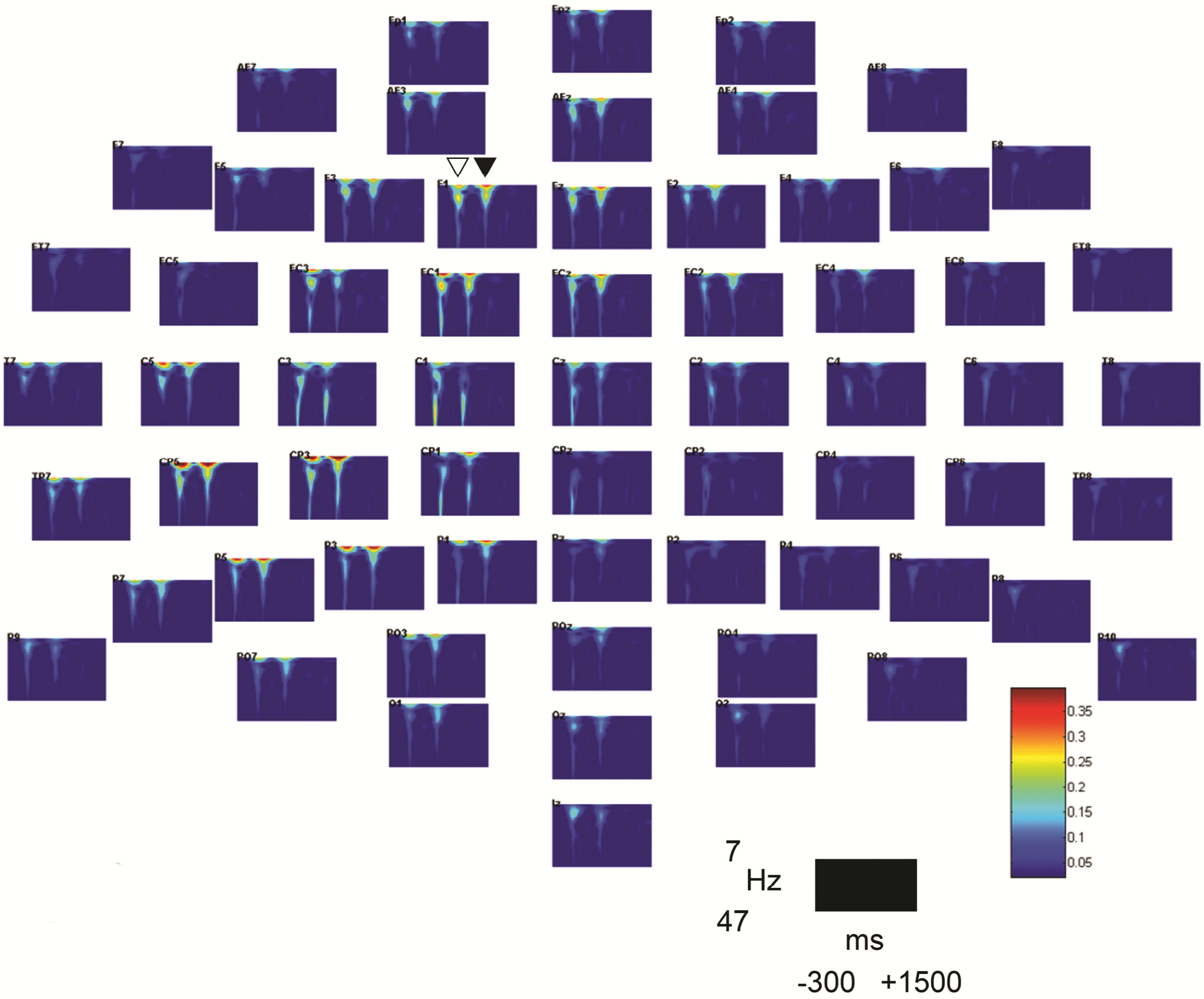


Figure 6. Time-frequency topography of the right hand proprioceptive EP
Grand average of the time-frequency transformed amplitude of the proprioceptive EP (avWT) shown across a long latency window, where the onset and offset effects are clearly seen. Stimulus onset is at 0 ms, offset at + 500 ms. N=14. Epochs total 8856 (VI).

motor integration to keep the handle steady even in the pauses between load changes.

Previously, somatosensory evoked gamma activity has been seen in studies of electric stimuli in the same region and latency range (44 ms for electric stimuli) [138]. In most other studies the data processing techniques makes the comparison impossible [101, 139-143]. In particular it has to be noted, that, presently, amplitude and ITPC is measured in each time (and frequency) point in comparison to mean field power or phase across a (wide) latency range, and phase consistency is here measured across trials not across electrodes.

The proprioceptive evoked potential: Functionality and constraints
The load stimulus evoked consistent contra-lateral cortical activity (I,II, IV,V,VII) which was called the proprioceptive EP. The frequency components corresponding to the EP had not been mapped previously, and before gamma activity had only been recorded after electrical stimuli. The load stimulus is a natural compound stimulus, which is simple to apply and it does not cause the anxiety in psychiatric subjects that electric nerve stimulation frequently does. The distribution of the waveform and frequency components of the proprioceptive EP suggested that activity was evoked in both primary and secondary somatosensory cortices as well as motor cortices and that part of it was the cortical "leg" of the long-latency stretch reflex.

The set-up was designed to enable a focus on proprioceptive sensation, not on movement or muscle tension and this worked although load discrimination was more difficult than expected.

The mechanical properties of the device induced limitations in it application: ISI had to be more than 1s and in the interpretation of evoked potentials and weight discrimination the simultaneous modulation of on/offset duration and force increment had to be taken into consideration.

Neither the relationship between load increment and EP amplitude/latency nor the relationship between muscle tension and EP amplitude/latency was mapped, as the focus was on the modulation of the EP by stimulus context. This restricted the later experiments to the 100g increment and instructions to have a relaxed grip.

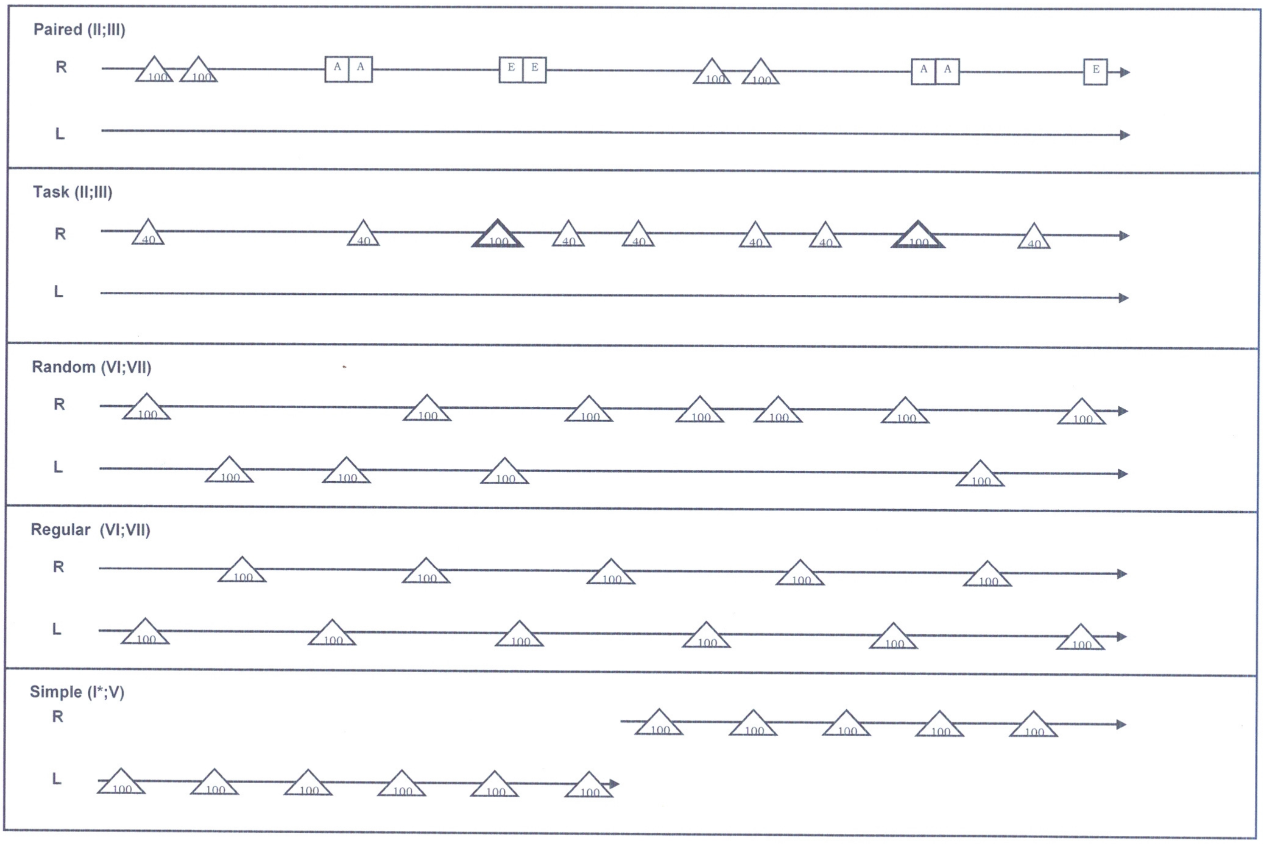


Figure 7. Stimulus sequences in the different paradigms
The proprioceptive stimulus was presented in a variety of sequences. Apart from the task sequence (panel 2) where the subject had to decide whether the weight increment was 40 g or 100 g, the stimulus was always a 100 g increment and all the EP or ERPs reported herein were evoked by a 100 g increment. In the early recordings (I, II, III) stimulus duration was 100 ms, in the later recordings (V, VI, VII) it was 500 ms to avoid overlapping offset potentials.
In panel 1 the sequence of auditory (A) and electrical (E) and proprioceptive (100) stimuli are shown. As indicated this was only recorded in the right hand (R). The cycle of stimuli was regular, lasting in total 12 s. In panel 2, please note the variability of ISI and the relative frequency of stimuli (1(100):4 (40)), the target being heavy and rare. In panel 3, please note the variability of ISI and random shifting of hand of stimulation in the Random condition, while the regular alternation is seen in panel 4. Simple repetitive stimulation was applied in the very first recording, *) although only in the right hand, while the later investigation of high frequency activity was performed in both hands, see panel 5.

Future work on and improvements of the load stimulus
As noted above mapping of the relationship between load increment and EP amplitude/latency and the relationship between muscle tension and EP amplitude/latency and perceived heavi ness would be necessary if future research focuses on the physiological aspects of proprioception. For this mapping it could also be relevant to be able to expand the maximum capacity of the spool – requiring another spool size.

If the device should be more widely used the set-up could be improved by the construction of a more fixed placement of the hand adequately designed to maintain hand and arm position yet allowing the elasticity of the muscle extension, and at the same time individually adjustable in many directions allowing comfortable posture in all individuals.

The precise localization of the evoked activity could be investigated through functional imaging during weight discrimination: This would increase the understanding of the regions involved in the EP and it might be possible to find correlations between evoked oscillations and regional blood flow changes that could substantiate the different stages in information processing.

Contextual modulation of proprioceptive event related potentials

Description of the applied experimental paradigms
After the initial verification that the load stimulus was able to evoke a measurable potential, the main idea was to include the stimulus in paradigms that could yield specific information as to what stage of information processing that might be abnormal in schizophrenia. An illustration of the different stimulus presentation sequences is given in figure 7.

The cognitive part of information processing was investigated in an odd-ball paradigm resembling a well-described paradigm for P300 recording. Consequently the first series of experiments focused on presentation of load increments of 40 and 100 g presented in a pseudo random series of stimulus presentations in the right hand, where the subject had to count the designated rare (1:4) target (3 runs where the 40 g increment was the target and three runs where the 100 g increment was the target) see figure 7, second panel (II, III).

The earlier pre-attentive stage of information processing was investigated by paired stimulation of the right hand by load changes of 100g presented with an ISI of 1s. The stimulus pairs were presented in a loop with two other types of stimuli (auditory and electric nerve stimulation). This resulted in an inter train pause of 3.5 s between the preceding median nerve stimulation and the first load stimulus of the pair, while the time elapsed since an identical load stimulus was presented was 12 s. See figure 7, top panel. The sequence of stimuli was fixed and totally regular. Maximum load lasted 100ms in each stimulus. No task was applied (II, III).

The last paradigm applied was designed to test the effect of regular vs. random presentation of the proprioceptive stimulus. The hypothesis, that regularity would induce a larger early cortical activity due to an increase in cortical priming, was inspired by earlier reports of cortical priming increasing somatosensory contra-lateral P40 through modulation of focus of attention [144]. The subjects had loads in both hands and regular alternation of hand of stimulation was compared to a stimulus sequence where a random function determined the hand of stimulation. The load change of 100 g lasted 500 ms and the ISI was fixed 1.5 s in the regular sequence and variable 1.2-1.8 s in the random sequence. See figure 7, panel 3 and 4. No task was applied (VI,VII).

Results of context manipulations on the different proprioceptive components

The middle latency contra-lateral parietal broadband activity at latency 60-80 ms was insensitive to repetition effects (II), see figure 4. It was not measured in the load discrimination paradigm. The activity was delayed and attenuated in those subjects who had many errors in the load discrimination task (II). The gamma frequency component (25-45 Hz) observed in the same region and at the same latency diminished from onset to offset of the load stimulus (VI, VII).

The broadband parietal central P100 diminished with repetition and it did not differ between the good or bad performers in the load discrimination task. It was not measured in the load discrimination paradigm.

The lateral parietal evoked beta activity (19-22 Hz) observed in the same time range (90-110 ms) was larger in the regular compared to the random condition, while the more low frequency activity (12-14 Hz) was unaffected by this. The regularity effect on beta activity in the 90-110 ms range was seen both at onset and offset of the stimulus, see figure 8, and at the onset particularly at run two (VI). These two frequency components as well as the two frequency components observed in the latency range 110-125 ms (14-15 Hz and 7-8 Hz) all diminished from onset to offset of the stimulus (VI).

The frontal N160 and central P200 diminished with repetition and increased in the target condition (II). They did not differ between the good or bad performers in the load discrimination task.

The parietal P360 and the wide-spread N500 were both augmented in the right hand target condition, see figure 9 (II). These components were not measured in the paired stimulus paradigm (II). Frontal negative activity in the latency range 300-400 ms was increased in the regular condition following right hand stimulation (VI).

Methodological issues related to the experimental paradigms

The design of experimental paradigms including the proprioceptive stimulus is heavily constrained by the low voltage of the potential, which necessitated a large number of epochs. For the time-series EP more than 250 epochs and for the time-frequency analysis at least 80 epochs had to be included (I, V)

Boredom or drowsiness was expected problems across the many trials in no-task paradigms, and to prevent that the experiment schedules were designed to spread out the same type of run across the day or the recordings were performed across two or three days (II, III,V-VII).

Habituation across the recording period was another possible effect of the many repeats. It was not possible to test this in the first experiments (I, II) where every acceptable epoch had to be included in the averages due to the low signal to noise ratio. In the later multi-run recording (VI) habituation effects were assessed across the recording runs.

Two of the time-frequency components (contra-lateral beta 18-28 Hz, 80-120 ms, and wide-spread alpha 7-10 Hz, 70-150 ms) attenuated across recording time. The beta component diminished primarily from the first to the second run. As the stimulus paradigms were identical in each run, this was not an effect of refractoriness but probably an effect of diminishing arousal level during the recording session. The early components were not modulated in this manner, suggesting that later processes were more susceptible to either diminishing arousal level or fatigue.

The load discrimination task was not associated with boredom, but several subjects complained of the difficulty, which also was substantiated by the large variation in counting errors. The subjects counted silently the target load and this made it impossible to sort the trials by correct response or even to know, if it was the targets they had counted. Furthermore, count errors might arise from difficulty in keeping track of the number instead of difficulty in weight discrimination. Still the alternative: to have a response button would also lead to problems due to the movement related potential, it would induce. In the first recordings of the load stimulus, it was pertinent not to have the ERP confounded by a movement related potential.

The regular vs. random paradigm included an inevitable problem as the regular sequence differed from the random sequence not only by predictability of the side of the next stimulus, but also by the duration of the interval between stimuli in the same hand. In the regular sequence same-side stimulus always had an ISI of 4 s (Right hand stimulus 0.5 s + ISI 1.5 s + left hand stimulus 0.5 s + ISI 1.5 s), while same-side stimulus could happen with different ISI (1.7 s-11.5 s) in the random condition depending on the random function. The beta component in the latency range 80-120 ms was attenuated in the random condition while none of the two later components were reduced. In the offset situation the stimulus was preceded by the same-sided stimulus (the onset) with exactly identical ISI (500 ms). Somatosensory refractoriness effects mainly depend on the immediately preceding stimulus and interval [99, 100], and consequently the amplitude difference between regular and random stimuli observed at offset, could not be due to difference in recovery cycle processes, but instead could be interpreted as facilitation of the regular stimulus.

Regrettably, temporal jitter was induced on the ISI in the random condition. This was meant to increase the difference in predictability by including both temporal and spatial uncertainties, but as the set-up was not designed to disentangle these two types of effects, it merely confounded the results. The difference in temporal predictability might have diminished the phase resetting due to diminished allocation of attention to stimulus onset. However, the main effect of stimulus paradigm on ITPC was on the offset, which should be unaffected by this variability.

Furthermore, the particular onset amplitude increase observed at the second run could be due to the debriefing questions

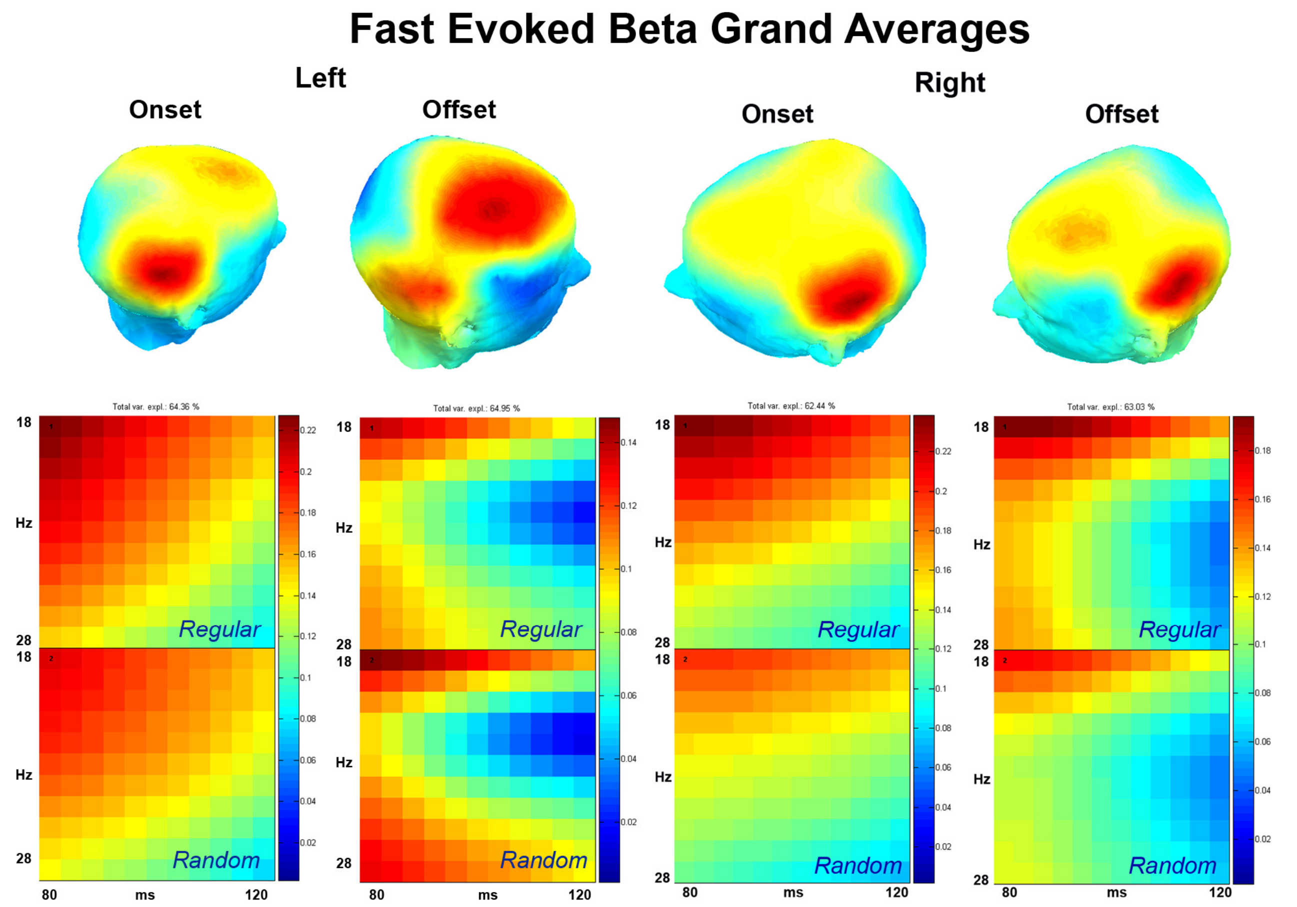


Figure 8. Increased parietal activity in the Regular condition in healthy volunteers
The grand average results of non-negative matrix decomposition when asking for one component in the time range 80-120ms and frequency range 18-28Hz of the proprioceptive EP. The averages were made across all subjects and all runs i.e. including 4428 epochs in each condition. While the analyses of individual files were performed in two regions (contra-lateral and ipsi-lateral), which were identically affected by condition, these illustrative analyses was performed across the entire 64 channels. Please note different colour scaling in on- and offset (VI).

posed in the break between runs after the first run of both condition. The questions were open-ended: "How did you perceive the stimuli, was there any difference between stimuli in the two runs?" The subjects perceived no difference in the stimuli as such, but they noted the difference in stimulus rhythm. The questions would be apt to increase awareness of the difference in paradigm, which could lead to increased top-down facilitation in the subsequent recording, particularly in the onset as observed.

Comparison to previous somatosensory paradigms
The finding that neither parietal P60 nor frontal N70 were affected by repetition was in agreement with the findings in the simultaneous recordings of the median nerve SEP P50 (measured as baseline to peak) [2], but not with the findings of a study of tactile and vibratory stimuli to the fingers [99]. The early proprioceptive evoked time-frequency components attenuated from onset to offset of stimulus. Although part of the same stimulus, onset and offset can be understood as separate events entering the somatosensory cortex after a pause similar to an ISI, and as such susceptible to the attenuating effect of a refractory period. In this case the findings would be comparable to investigations of paired stimulation where the ISI was 500 ms. Repetition effect of this ISI was previously observed on the peak-to-peak measured vertex amplitude in the time range 50-100 ms [101, 145], and the contra-lateral activity in the 40-60 ms range also attenuated during repetitive stimulation with ISI of 450 and 800 ms [146].

One study, measuring somatosensory evoked activity at vertex, reported that beta activity was more sensitive to repetition than gamma activity [101], which is in agreement with the finding of larger difference between onset and offset in contra-lateral beta than the gamma activity (VII).

The attention related proprioceptive P360 was smaller and later than previously reported somatosensory P300 [147-154] probably due to the task difficulty, which is a major determinant of the P300 waveform amplitude [155].

In single trial recordings, it has been shown that early cognitive components (40-100 ms), repeatedly observed to be modified by sustained focal attention [156-158], also appear, when the stimulus do not reach awareness [159]. This suggests that the components characterized as endogenous or cognitive could be modulated without effort or even awareness of the subject. Tomberg and Desmedt suggested that the earliest cognitive modulation (40-60 ms) was a manifestation of priming of areas in the primary somatosensory cortex, facilitating the subsequent processing [160]. The somatic priming was considered to emerge through interactions with the dorsolateral prefrontal cortex [159].

The cognitive modulation in the 40 ms time range was observed in studies of electrical stimulation; the evoked activity following the proprioceptive stimulus would be delayed compared to this due to mechanical properties of the stimulation. Like the above described P40 modulation [160], increased P60-70 amplitude of the proprioceptive EP was associated with increased perceptual efficiency (II). The evoked beta activity (19-22 Hz) observed in the 90-110 ms time range was larger in the regular stimulus sequence compared to the random sequence (VI).

Following the above mentioned trail of thoughts, it is suggested that the beta amplitude difference was a manifestation of facilitating effects in the regular condition. It has been consistently shown that both voluntary sustained (focused on location for a lengthier period) [144, 159-161] and transient (shifting focus from trial to trial) [157, 162] spatial attention increases the middle latency somatosensory ERP. Moreover, it has also been shown that attention to a point in time will increase amplitude of the brain response at around 100 ms post-stimulus [163].

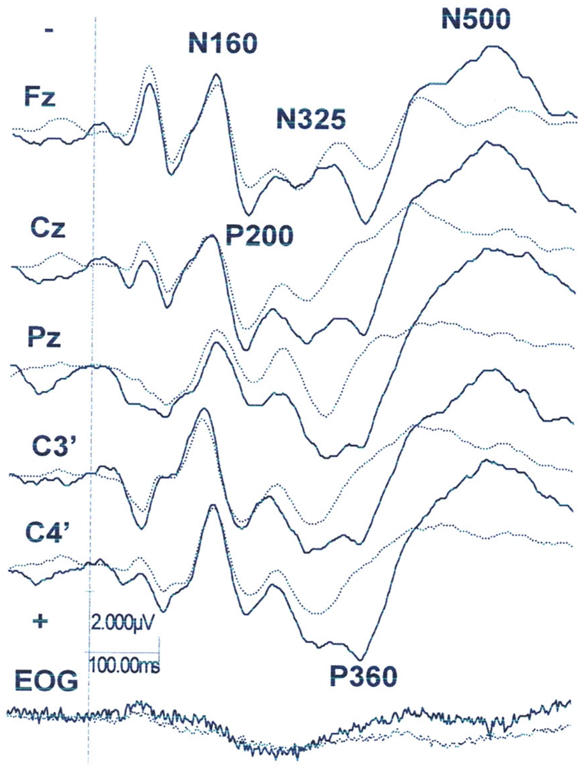


Figure 9. Proprioceptive P300 in healthy volunteers
Grand averages of the proprioceptive ERP in the task condition (second panel in figure 7). Stimulus is 100 g weight increment. Stimulus onset corresponds to the y-axis. Band-pass 0.05-30 Hz. Target: Solid. Standard: Dotted. N=24. N160, N325 and N500 were maximal in the frontal (Fz) lead, P200 was maximal at vertex (Cz) and P360 was maximal in the central parietal (Pz) lead (II).

Facilitation of contra-lateral parietal or frontal central SEP amplitude in the latency range 70-120 ms due to voluntary task-related sustained spatial attention has frequently been reported [144, 158, 162, 164, 165]. While sustained attention modified electrically evoked somatosensory ERP activity as early as 40 ms post stimulus, trial-to-trial cued shift of spatial attention from hand to hand using tactile stimuli, specifically modulated activity in the contra-lateral parietal region in the 70-125 ms latency range [162]. This latter finding could be very relevant for the present study, where the observed modulation of beta activity in the 90-100 ms range could be a manifestation of shifts of attention induced by the regular sequence of hand alternation, where any stimulus served both as stimulus and cue.

The random condition mostly resembled the stimulus sequences in studies of passive attention, where attention-like processing is triggered reflexively by a stimulus either delivered in silence or deviating from a series of identical stimuli [164]. Frontal and parietal activity in the 70-110 ms range is augmented by the deviant stimulus; the same activity is also modulated by active attention [164-166]. This modulation is seen as a manifestation of the attention capturing effect of deviant, infrequent or unexpected stimuli [165]. If this type of facilitation was induced in the present experimental paradigms, increased activity would be expected in the random condition. The opposite effect was observed (VI), and later activity was not enhanced as would have been expected in this case.

Consequently, the facilitated contra-lateral and slightly ipsilateral parietal beta activity observed 90-100 ms after both onset and offset of the proprioceptive stimulus in the regular condition is interpreted as a manifestation of involuntary shift of spatial attention cued by each stimulus and effectuated through top-down priming (VI). Moreover, it has to be considered that the proprioceptive stimulus was a perturbation of a hand posture and as such initiated reflex postural correction. Parietal activity at latency 80 ms was enhanced when an electric stimulus was a trigger for the movement of the same hand [167], a condition comparable to the present posture correction.

In the above mentioned reports the evoked activity was not subdivided by frequency content, and phase precision of the response was not examined. Phase precision naturally enhances the average evoked amplitude. The proprioceptive ITPC was modulated in the same manner as the amplitude measure suggesting that at least part of and perhaps all of the amplitude increase was a manifestation of increased phase precision of the oscillations (VI).

It has previously been observed that activity of the secondary somatosensory cortices (SII) have a bilateral distribution, where the contra-lateral activity is more prominent than the ipsi-lateral [168]. Following this and considering the time range, the bi-lateral parietal distribution and the onset/offset attenuation, it is suggested that the parietal beta activity arise primarily in the secondary somatosensory cortices (VI).

Conclusion on the findings of contextual modulation and constraints

The traditional paradigms applied were efficient for uncovering modulations by repetition and attention. The early part of the brain processes initiated by the load stimulus were not quite identical to those observed using tactile stimuli, but the later components (100ms<) conformed to the pattern of modulation otherwise seen in somatosensory ERPs. The later components were very sensitive to repetition and modulation of attention. Delayed P60 and attenuated N70 were seen in those subjects who had the highest number of errors, along with diminished P360 and N500. The latter finding could indicate that specific proprioceptive feature extraction was accomplished within the first 100 ms post-stimulus or it could be an indication of diminished allocation of attention.

When the proprioceptive evoked activity was subdivided by time-frequency signature the beta frequency cross-hemisphere parietal subset of the evoked activity had increased amplitude and ITPC in the regular condition (VI). The effect of regularity was suggested to be imposed by top-down priming of ipsi- and contralateral secondary somatosensory cortices due to the more predictable situation. However, some confounding effects might be at work in the regular vs. random paradigm, which demand precaution in the interpretation.

Future work and improvements of stimulus paradigms

Several lines of further work could be pursued. As to the effect of regularity, the fact that the paradigm involved regularity of hand alternation might be crucial for the distribution of the activity and the frequency pattern. It would be necessary in future studies to examine whether regularity differences across unilateral paradigms yield corresponding modulation of beta frequency activity. Likewise, in further studies the effects of temporal predictability and ISI could be disentangled through a more elaborate experimental design.

Furthermore, the suggested allocation of involuntary attention could be explored in an experiment comparing the modulation of the beta time-frequency component as evoked by regularity to the modulation induced by voluntary allocation of spatial attention.

Another route could be to develop a paradigm, which might be designed as a go/no-go or forced choice response paradigm, for weight discrimination of increasing difficulty. The go/no-go paradigm includes equal number of the two included types of stimuli and this is a feasible way to achieve many epochs in a cognitive paradigm. At the same time, the activity is uncontaminated by the effects of difference in stimulus frequency. This should make it possible to map the early components in a paradigm where weight discrimination could be assessed. It would be contaminated by the movement potential, but having more electrodes and the possibility of disentangling the activity through the multi-way decompositions (see below), an additional recording of the button press could solve the problem. This could also be applied in the left hand, which was less explored in the first experiments.

Another improvement could be to make the load stimulus a feed-back feature in a combined paradigm including an auditory or visual task. It could either be the load increment or the hand of stimulation that could carry the feedback information. This would focus attention on the weight sensation without making a task of it. More work in this direction also needs to investigate the optimal interval between task stimulus and feedback.

Factor analyses of event related EEG data

The developments presented in this paragraph were achieved in collaboration with Morten Mørup, PhD, Informatics and Mathematical Modeling, Technical University of Denmark.

The results of this collaboration are briefly described as the methods are basic to the results of the later experiments. However, note that the entire programming and mathematical development was the work of Morten Mørup and my contribution was on the conceptual and application level.

Validating the application of factor analyses

The first experiments were recorded with seven electrodes placed according to the International 10-20 System at FP1, FP2, Fz, Cz, Pz, C3´, and C4´, the last two placed 2cm posterior to C3 and C4 above the somatosensory cortices (I,II,III). The small number of electrodes made it impossible to make scalp topographies and it made any localisation very crude. The data processing was quite conventional, averaging the time-series data and subsequent making visual peak detection of the individual EPs after criteria defined by the grand averages (I, II, III). As the research progressed, it was possible to obtain a full cap of 64 electrodes (IV-VII).

The prime focus changed to the mapping of early activity subdivided by frequency content, the data was wavelet transformed 1, [169](IV-VII). Following wavelet transformation the event related data was multi-dimensional: channel x frequency x time and when the effect of condition or subject grouping was added: channel x frequency x time x condition/subject. The event related EEG data was subsequent decomposed by a multi-way factor analysis, the parallel factor analysis (PARAFAC) (IV) and further developments of multi-way and matrix factor analyses [117, 170, 171] (V-VII). Initially, the results of visual peak detection of individual subject file decompositions and the multi-file PARAFAC analyses were compared to previous obtained results of a visual task paradigm [172, 173], (IV) and later the newly developed non-negative matrix and multi-way analyses [170] were compared to visual peak detection of the maximum ITPC value in the plot of 64 channels x frequency x time (V).

Results of the multi-way and matrix analyses

Both the initial PARAFAC and the non-negative multi-way decompositions seem well-suited for initial data exploration. Both of the non-negative factor analyses could decompose and present data intelligible. Exploratory five-way PARAFAC analysis (channel x frequency x time x condition x subject) of ITPC resulted in two components where the first component was attenuated in one of the conditions, as expected by previous research [172, 173]. A second component, not previously described, was only seen in one of the stimuli conditions. Manuel read-off of the result of subsequent individual three-way PARAFAC analyses confirmed the exploratory findings regarding the first component (IV).

The non-negative matrix factorization analysis (NMF) (170 at http://www2.imm.dtu.dk/~mm/) was a matrix analysis like the independent component analysis 110 but without negative values. This analysis results in regional specific components supplemented with individual time-frequency patterns.

NMF analysis correlated well with the result of visual peak detection performed across the entire electrode array of time-frequency maps, while the non-negative multi-way factorization (NMWF), a PARAFAC extension, did not (V). The NMF was applied in the later analyses and the similarity of components across hand of stimulation and subject samples substantiated that the model captured physiologically separable processes. The subdivision of the evoked activity was substantiated by the different modulation of the components by stimulus paradigm and run order (V-VII).

Methodological issues related to the factor analyses

The three-way PARAFAC analysis could have been investigated using two-dimensional factor analysis models by unfolding one modality to the other. But it is noteworthy that the results of the multi-way PARAFAC analysis could not be obtained by unfolding the array to a matrix. In this case, at least one of the factor analysis' modalities would represent three of the original modalities which would make the factor components hard to interpret.

However due to the variability both in frequency, latency and location, it is always a question whether an activity measured in one individual is the same as an activity slightly altered in all dimensions in another individual. In the description of evoked or event related potentials the grand average appearance has been the customary way to define components 20. The exploratory PARAFAC/NMWF analyses corresponded to this procedure, and the analysis had the same weakness as a grand average: a few subjects with very large activity might have a large impact on the component or peak shape. Indeed, the very strong assumption of PARAFAC/NMWF that identical activity is to be found across subjects is questionable (IV). The low correlation of the NMWF to the result of visual peak detection might be due to large variation in time-frequency location of the activities across subjects, making the NMWF model too restrictive (IV). The NMF model has more free parameters than the NMWF model and thus can better describe data in accordance with the results of visual inspection (IV).

The expansion of the algorithms particularly extended the possibility for decomposition into the frequency domain, while topography was given less weight. As the decomposition algorithms yielded as many components as asked for, it was a decision to select the criteria for a successful model. The helpful feature in this process was the mapping of a time-frequency signature as a across channel collapse, which was easy to compare across components, and, if too many components were asked for, the emergence of components with a peripheral "patchy" topography and a diffuse time-frequency map, which was considered to be due to minor physiological artefacts.

Initially, the individual maximum values of two time-frequency components were extracted from analyses spanning a window of 25-80 Hz and 0-200 ms (V), but as wider frequency ranges were investigated and five components emerged the analyses did not perform well in the extraction of maximum values (VI-VII).

Consequently, it was necessary to perform the multi-file decompositions in a narrow window only encompassing one component as defined by the exploratory analyses of the full data set of healthy subjects (VI). Some components had a bifocal distribution in the exploratory analyses (VI), which made it difficult to perform a regional component separation by the multi-subject analyses. As the time-frequency signature was the same across the regions, it was not possible by extension of the component number to separate the activities. Instead the analyses were performed across selected large scale regions (anterior/posterior or ipsi-lateral/contra-lateral). See figure 10 for an illustration of the procedure.

Specific pre-processing of data for the analyses was necessary to avoid systematic artefacts like the 50 Hz line noise or single electrode instability, particularly when analyzing the amplitude measures. Several options for notch filtering and baseline correction were investigated before normalization of the amplitude measure circumvented the problems of hard-ware artefacts (VI-VII).

Brief exposition of factor analyses used in EEG research

PARAFAC is a decomposition of large data matrices mostly used in chemistry. It was only recently used for EEG data [174], and only in a very limited way in ERP research [175, 176]. The limitations of the prior use of the method were the lack of computer memory and constraints due to lack of pre-processing of data. The presently derived components were based on a time-frequency x channel decomposition of the EEG in opposition to mostly applied information based signal processing that were based on channel x time decompositions like the principal component analysis (PCA) or independent component analyses (ICA) [177, 178]. By the addition of an extra dimension it was possible to investigate topography and time-frequency pattern in one analysis. Previously a priori selection of either location (single electrode activity or a regional collapse of several electrodes) or time-frequency range was the method for visualization of oscillatory activity 1. Recently, it was suggested that wavelet transformation should be performed on each single component after ICA pre-processing [179, 180]; the procedure applied here is another combination of the procedures as the data are wavelet transformed first following a procedure similar to the one used for gamma activity mapping 1 and then blind source separation is applied through the time-frequency x channel factor analysis.

Applicability and constraints in the use of factor analyses for the time-frequency transformed EEG data

The multi-way analysis served well as an exploratory tool for wavelet transformed event related EEG. The analysis was able to extract the expected features of a previously reported ERP paradigm (IV).

The NMF analysis could be applied both for exploratory and confirmatory analyses. The NMF analyses performed like visual peak detection in the detection of maximum activity and made it possible to extract maximum values corresponding to specific time-frequency components across a large array of files. When the NMF analysis was used for data exploration it could span a wide time-frequency range, but for data extraction narrower windows of interest were necessary (VI-VII). Stability of the solutions required substantial data pre-processing and presently the number of oscillatory components were determined by externally defined criteria.

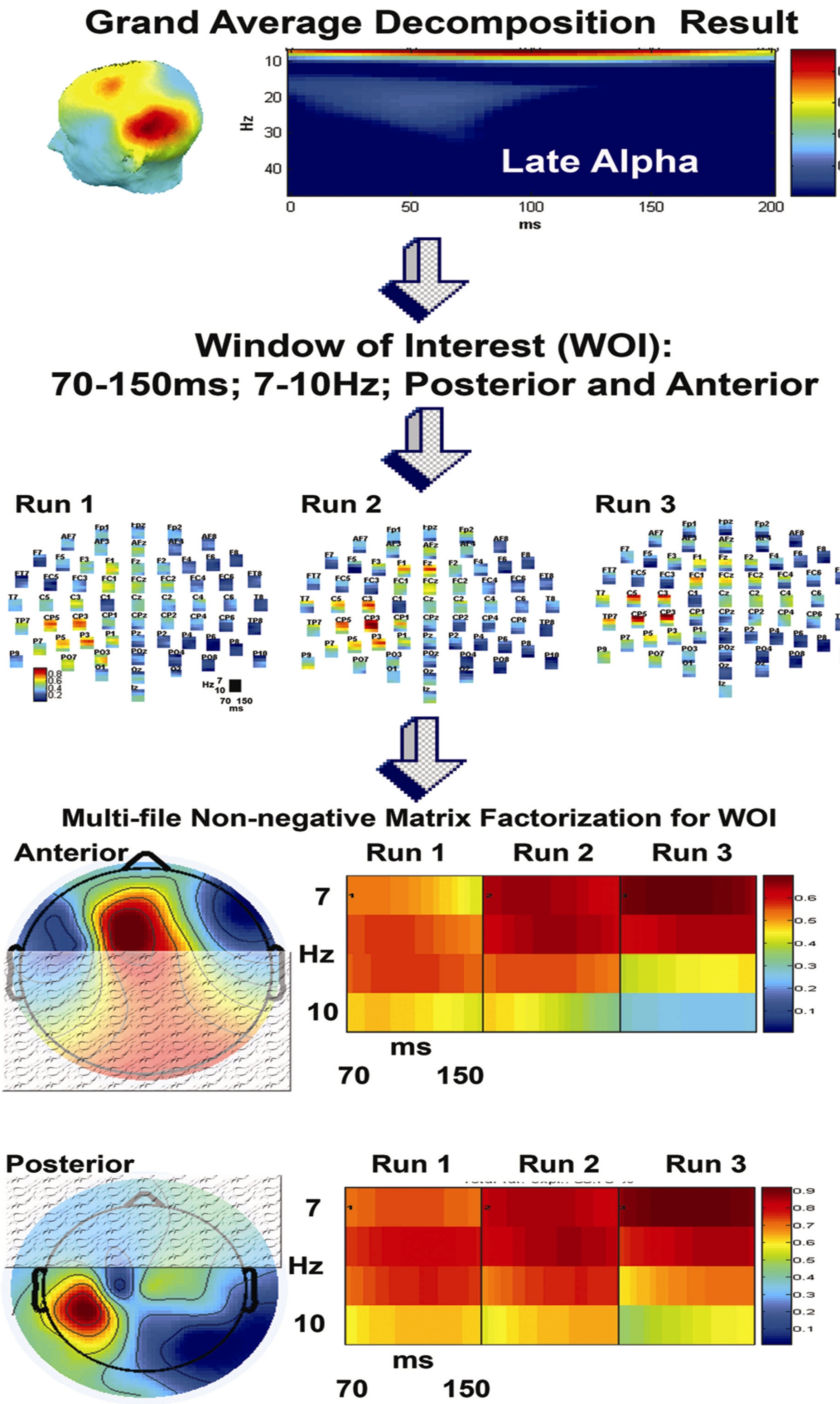
Future work and improvements of factor analyses for event related EEG

Dipole source modelling could not presently be applied on measures derived from phase information i.e. the ITPC. The complicated algorithms are designed to work with intensity aspects of the oscillations, i.e. power, based on knowledge of how amplitude changes is transmitted in the tissues of the head. Source location is derived via elaborate statistical models trying to solve the "backward" problem inherent in the analyses [181]. To integrate dipole source modelling with the multi-way decompositions would be a challenge for further mathematical-physiological collaborations.

Another area of future research would be to integrate values like cognitive or psychopathological scores into the multi-dimensional analyses and in this way derive frequency component signatures that are relevant for specific individual traits.

Figure 10, next page. Flow-chart of application of the non-negative matrix analysis

An example of data extraction in one time-frequency amplitude component in one subject (subject 5). The window of interest (WOI) is based on an exploratory decomposition or prior results reported in the literature. An example of a component resulting from an exploratory analysis is seen in the top row: the late alpha component following the onset of the right hand stimulus. The original time-frequency topographies of the three runs of subject 5 are shown in the third row. At bottom the two regional decompositions are shown, asking for one component in the narrow WOI. In opposition to the illustrated example here, the applied analyses span all files of all subjects in both conditions in one WOI (VI).



Grand Average Decomposition Result
Late Alpha
Hz
ms
Window of Interest (WOI):
70-150ms; 7-10Hz; Posterior and Anterior
Run 1
Run 2
Run 3
Multi-file Non-negative Matrix Factorization for WOI
Anterior
Posterior
Hz
ms
70
150

Table 1. Patients and Comparison Subjects in the Clinical Investigations

COM: Age- and gender matched healthy comparaison subjects; SZ Schizophrenia patients SZS: Schizophrenia Spectrum patients. RT: Reaction Time. Choice: One-back task of ascending numbers. Mean value with * when difference between COM and SZS was significant in Students t-test (p<0.05).

Variables	Clinical Sample 1 (III) COM		Clinical Sample 1 (III) SZ		Clinical Sample 2 (VII) COM		Clinical Sample 2 (VII) SZ	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Age (years)	29	8	28	7	28	7	28	6
Cigarettes pr week	36	47	75	78	24	38	64	73
Simple RT	341	84	341	64	336	90	334	99
Choice RT	568	101	628	61	515	86	586*	113

5. MAIN CLINICAL FINDINGS AND DISCUSSION

Brief description of main findings

Twelve male schizophrenic patients demonstrated abnormalities in proprioceptive information processing measured as proprioceptive ERP's. When the load stimulus was delivered as the first of a pair in the context of a very regular loop, the early contra lateral parietal activity was delayed, and the successive P200 had increased amplitude. At the second stimulus the early frontal activity, probably arising as part of the long-latency response, was increased in amplitude (III). See figure 11. The abnormalities were not correlated to load discrimination task performance. Neither proprioceptive task P300 nor P100, N160 or P200 gating differed between these patients and healthy comparison subjects (III).

The patients were not in acute psychotic exacerbation and they had no major cognitive deficits or prolonged reaction time. See table 1, for a comparison of the patients and their matched comparison subjects, and table 2 for a comparison of the psychopathology of the included patients.

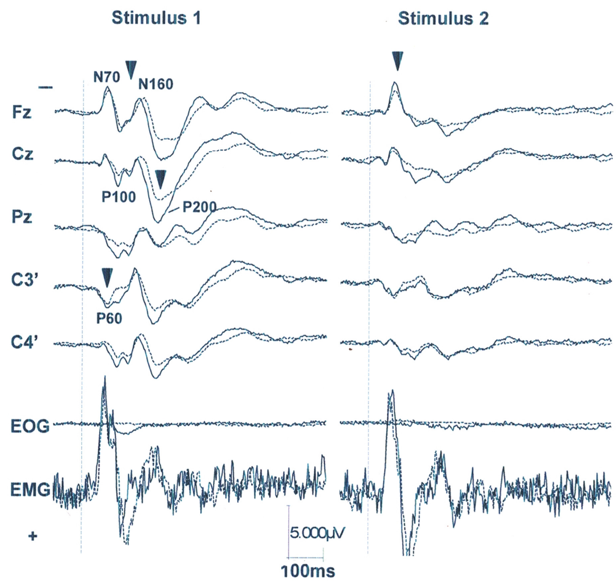


Figure 11. The difference between schizophrenic patients and healthy comparison subjects in the simple propriocetive EP
The EPs were recorded in the paired stimulus paradigm, see figure 7, top panel. The event was identical in both situations: A 100g load increase in the right hand, duration 100 ms. Event onset is marked by the y-axis. Comparison subjects (N=24): Dashed. Schizophrenia subjects (N=12): Solid. Solid arrows points at peaks differing between patients and comparison subjects. Frontal central (Fz), vertex (Cz), parietal central (Pz) contra-lateral parietal (C3'), ipsilateral parietal (C4') electroculogram (EOG) and EMG of the forearm extensor muscles (unpublished – II).

A mixed gender sample of 18 schizophrenic and schizotypal personality disorder patients (8:10) demonstrated abnormalities in proprioceptive information processing measured as proprioceptive evoked oscillations (VII). The frequency range of the investigation in this sample was narrowed as it only included the beta and gamma frequency range. In consequence only three components emerged in the exploratory matrix analyses (VII), see figure 12. These components resembled those previously observed in the healthy subject sample (V, VI), see figure 5, for a comparison, although the frontal beta (figure 12) might include activity that in the 5-component model was included in the early alpha-beta component (figure 5). The contra-lateral beta activity was denominated fast beta in the first study (VI, figure 5). The attenuation of amplitude and phase consistency observed in all components from onset to offset of the stimulus in healthy subjects (VI) was reproduced and this attenuation was seen in both subject groups (VII). The multi channel ERPs also showed a consistent pattern across the two studies, although the ERPs comparing the mixed patient sample with the matched comparison subjects (VII), see figure 13, had a slow positive trend that was not seen in the first multi channel ERP (VI).

The patients had generally attenuated amplitude of contra-lateral high frequency (18-45 Hz) activity in the 40-120 ms latency range. ITPC showed a corresponding attenuation. Frontal beta activity in the slightly later time period (100-150 ms) and lower frequency range (14-24 Hz) did not differ across any of the two groups (VII). Looking at the different diagnoses of the patients, the schizotypal patients had general gamma (25-45 Hz) amplitude attenuation, while both patient groups had a specific left hemisphere gamma amplitude attenuation. This was observed at onset of the load stimulus in the right hand in the regular, predictable, condition, see figure 14 (VII). Left hemisphere gamma activity was also particularly enhanced in the comparison subjects at onset in the regular condition compared to the random condition.See figure 7, panel 3 and 4, for an illustration of the different conditions. That the deviant findings were more circumscribed in the schizophrenic than the schizotypal patients was unexpected.

Methodological issues specific to the clinical studies

The first patient sample consisted of twelve un-medicated right handed schizophrenic male patients (III). The age range was wide (18-49 years) and so was the duration of illness (0.5-23 years); in this way it was not a very uniform sample. On the other hand, the patients all lived by themselves and they managed to do so as none of them was send to hospital due to their lack of medicine compliance. They had low scores of psychotic symptoms and consequently the abnormalities observed could not be attributed to psychotic derangement. However, the cognitive screening and the reaction time measurement were brief tests. More elaborate neuropsychological testing could have revealed more deficiencies. Regrettably only the right hand was examined in (III). This

Table 2 Psychopathology of the schizophrenia spectrum patients

*) SZ (III): Schizophrenic subjects of the first clinical investigation, all without medication for at least one month prior to the EEG recording; SZ (VII): Schizophrenic subjects of the second clinical investigation, three without medication, of these two were drug-naïve. SPD: Schizotypal Personality Disorder patients of the second clinical investigation, one without medication. Std: Standard deviation. SAPS: Scale for Assessment of Positive Symptoms. SANS: Scale for Assessment of Negative Symptoms.

	SZ (III) N= 12, 0 females		SZ (VII) N= 8, 6 females		SZ (III) N= 10, 5 females	
	Mean	Std	Mean	Std	Mean	Std
Total number of months of antipsychotic treatment	9,7	9,8	18,9	32,4	2,9	2,6
SAPS Positive Dimension	4,3	2,3	3,6	2,1	1,2	1,3
SANS Negative Dimension	6,8	4,5	8,0	5,0	5,3	3,0
SAPS/SANS Disoranized Dimen-sion	2,9	2,6	2,4	1,2	0,4	1,3

made it impossible to explore laterality aspects of early processing.

The second patient sample consisted of eight patients with schizophrenia and ten patients with schizotypal personality disorder (VII). Eleven patients were female, but apart from the mixed gender, it was a much more uniform sample with a mean age of 28 years (std 6 years), see table 1 for details. The patients were in a stabilization period of their first admittance, when they were tested. It was not ethically sustainable to leave them without medication. The schizotypal personality disorder patients were frequently treated with SSRI antidepressant medication at the time of admittance. Most studies of early gamma activity report no effect of antipsychotic medication neither through sample stratification [182] nor correlations with chlorpromazine equivalents [183-188]. Reduced gamma activity has been observed in an un-medicated patient sample and the only positive finding of medication effect has been an enhancement of early evoked gamma activity in patients receiving second generation antipsychotics compared to patients taking conventional antipsychotics [189]. Ten of the patients in the present sample received exclusively second generation antipsychotics and following the above finding, the primarily confounding effect of medication would be diminished group differences, not false group differences. While two schizotypal patients were un-medicated, the others received second generation antipsychotics. This makes it difficult to interpret the schizotypal vs. schizophrenia difference as an effect of medication.

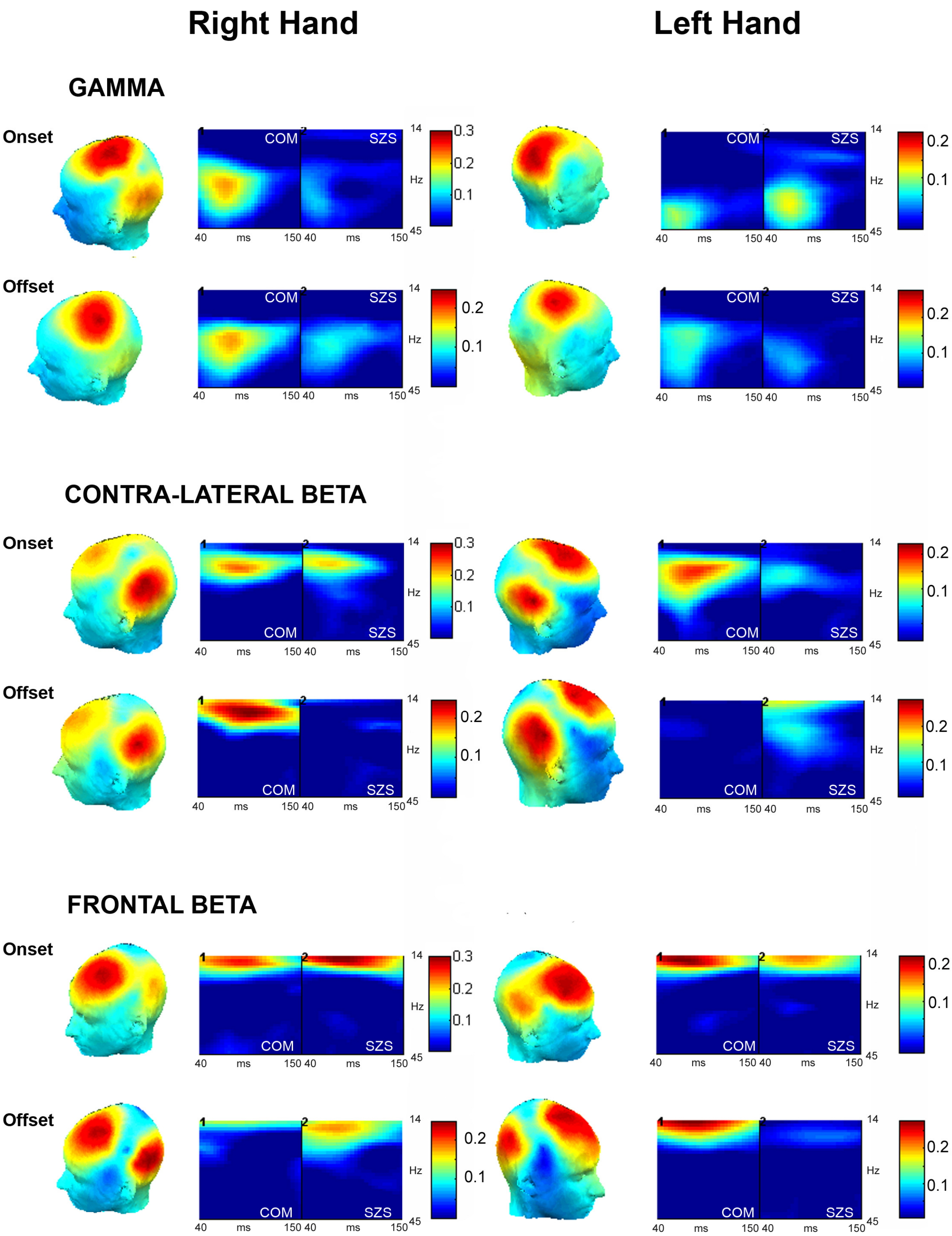
Obviously, the patient group was heterogeneous concerning the display of positive symptoms. Yet, apart from the DSM-IV criteria, diagnostic weight was given to symptoms of self-disorder to ensure that the schizotypal patients were schizophrenia spectrum patients [190-192]. In accordance with this, the two subgroups had trait features like negative symptoms in common, and they had been hospitalized for a comparable length of time. The finding of a more global dysfunction in the schizotypal patients was not expected as previous studies of cognition and information processing mostly have shown deficiencies in these patients in between the values of healthy and schizophrenic patients [193]. The possibility that this finding could be due to some specific psychopathology, which the schizotypal patients do not share with the schizophrenic patients, seems unlikely. It would have to be probed in future studies including a comparison group consisting of psychiatric patients with depression or anxiety.

The increased P200 amplitude in the chronic schizophrenic patients (III), see figure 11, page 34, was unexpected but it could reflect an increased orienting response as an indication of increased arousal [194-196]. The finding of a general gamma activity reduction in schizotypal patients compared to schizophrenic patients (VII) was also unexpected. Arousal disturbances in schizophrenic samples are well-known, some being hyper-aroused, some being hypo-aroused [197] and this makes the interpretation of the findings complex. Increased P200 amplitude in schizophrenic is not the most common finding. Following electric stimulation the most frequent finding is amplitude reduction [198-200]. Only a one study have reported increased P200 amplitude following electric stimulation [201].

As P200 normalized after the second stimulus of the pair, one plausible explanation could be that the faulty earlier stimulus processing, seen following the first stimulus, lead to an increased unspecific response. Another explanation could be inherent arousal abnormalities in the patient sample leading to an unspecific increased orienting response, which also would be expected to emerge at the first stimulus. Abnormal situational arousal, i.e. hyper arousal induced by the experimental procedures, could also explain the large P200 amplitude in the patients, but this was considered less plausible, considering the fact that the patients had been in the laboratory for two days of recording and they were well adjusted to the situation (III).

Visual evoked gamma activity in schizophrenic patients also seems to be modulated in a complex manner that might be related to arousal. Frontal gamma activity was observed to be re lated to arousal. Frontal gamma activity was observed to be reduced in a study of sustained attention using a continuous performance task [202], while the patients had increased activity at all task levels in a graded working memory task [203]. It was suggested that the schizophrenic patients had increased activity as if the task was new and effortful even when it was simple and repeated [203]. Considering the fact, that the schizotypal patients had a more general reduction of oscillatory activity than the schizophrenic patients (VII), this could reflect divergent abnormalities of arousal in the two samples. Recent findings in healthy volunteers have shown that gamma activity is very sensitive to the level of activity, and the modulation is contra-intuitive as low activity is accompanied by high gamma activity [204]. Regrettably, we did not measure skin conductance orienting response leaving the findings open to speculation.

In the first study in healthy subjects the regular, predictable, paradigm induced increased contra-lateral beta activity (VI). This effect was not seen in either subject group in the following patient study (VII). The first results were based on a lengthier recording session including three runs of each paradigm, and re-examination of the data showed that pair-wise comparison of only the first run data yielded no significant difference between



Right Hand
Left Hand
GAMMA
CONTRA-LATERAL BETA
FRONTAL BETA
Onset
Offset
COM
SZS
ms
Hz
40
150
14
45
0.3
0.2
0.1

Figure 12, previous page. The proprioceptive evoked potential decomposed across subject groups
After group collapse of the wavelet transformed amplitudes, three components were extracted in the latency window 40-150ms and frequency window 14-45Hz. The non-negative matrix analyses were performed for each hand and at onset and offset. The emerging three components were easily comparable across the four analyses. The collapsed data of the comparison subjects (2 (conditions) x 18 (subjects) x 108 epochs = 3888 epochs) (COM) and the schizophrenia spectrum patients (3888 epochs) (SZS) were included separately in the analyses, thereby creating separate time-frequency plots for each group, while the head plots at the left side show the common topography.

onset beta activation in the two paradigms (unpublished data). Hence, the results agreed with the previous findings in the first run in healthy subjects, but the study became inconclusive as to the effect of predictability on the contra-lateral beta activity in schizophrenia.

It is regrettable, that it was not possible to record more than one run in the patients. It was attempted but the patients could not tolerate a lengthier experiment due to restlessness, tiredness or inconvenience caused by the electrode cap. An attempt was made to circumvent this problem by introducing each paradigm with an explication of the type of stimulus sequence. This intervention, which was different from the first study, where the stimulus series were left unexplained, could have increased left hemisphere gamma activity in the healthy subjects (VII).

It is not straightforward to compare the latency delay observed in the patients in (III) with the gamma and beta components described in (VII). The time-frequency transformation, used for the evaluation of oscillatory components, diminishes the latency resolution making it impossible to judge, whether the oscillatory components were slightly delayed in the patients in (VII). On the other hand, the patients had diminished ITPC and this corresponds well with the fact that latency jitter of the response leads to broadening of the average waveform imparting a latency delay.

Lack of EMG differences between patients and healthy comparison subjects and lack of correlation between EMG and EP measures (III, VII) suggested that the abnormalities of the first contra-lateral parietal activity was not confounded by difference in muscle contraction. Furthermore, the finding of increased amplitude of P100 and P200 and unaffected N160 (III), and likewise un-affected late frontal beta activity (VII) in the patients also contradicted the notion that a peripheral intensity aspect of the stimulus could explain the findings.

Comparison to previous clinic research of somatosensory information processing

The proprioceptive processing aberrances observed here are localized to the left hemisphere. In the first study the left hand was not investigated making hemisphere comparison impossible. But focusing on left hemisphere abnormalities, the results add to the evidence of specific left hemisphere abnormalities in schizophrenia.

In a recent investigation of a task of voluntary button press [205], gamma activity was recorded at contra-lateral frontal central electrodes above motor cortex in healthy subjects and schizophrenic patients. While this gamma activity reflected motor preparation and as such was maximal above motor cortex, the presently reported proprioceptive activity was sensory evoked and accordingly maximal above contra-lateral parietal leads corresponding to the somatosensory cortex. Although the cortical origin and the tasks differed some parallels existed in the results: The left hemisphere gamma activity differed between comparison subjects and patients as the comparison subjects had larger premovement than post-movement gamma activity and the patients had no difference [205]. In the proprioceptive experiment the healthy subjects had larger evoked amplitude in the left hemisphere in the predictable sequence compared to the unpredictable sequence, and the patients had not. Whether this resemblance could be understood as an effect of a diminished corollary discharge in the patient group [13, 14, 206] or weakening of some other top-down contextual modulation cannot be answered by the present set-up. The task of pressing a button in a regular sequence at approximately every second, as seen in [205], is different from keeping a stable hand posture, carrying a load. However, the stable hand posture also demands voluntary sustained effort, and the expectation of the load perturbation, that should be counterbalanced by additional muscle force, seems similar to a preparation for a movement.

As also seen in the study by Ford and colleagues, gamma activity in the right hemisphere was not modulated in the healthy subjects in same manner as in the left hemisphere. This might be an effect of the well-known left>right cortical asymmetry of the somatosensory response in healthy subjects [207, 208] as well as the more diffuse topography observed in the right hemisphere [209]. Considering that, it is difficult to interpret the result as an indication of asymmetrical hemisphere involvement in the patients, even though attenuation of left hemisphere gamma has previously been observed in auditory studies [185, 187] and some brain imaging studies have reported abnormal hemisphere asymmetry of somatosensory cortices [66, 210-212]. As other studies show reduced right hemisphere gamma activity in patients with schizophrenia [106, 213, 214], it is not possible to arrive at a conclusion. It seems most justifiable to understand the results in terms of a specific increase of left hemisphere evoked gamma in the regular sequence in the healthy subjects, an increase that the patients are not able to generate because of lack of top-down modulation.

Somatosensory evoked gamma activity in schizophrenic patients has not been described elsewhere. Somatosensory EPs following electric stimulation has previously been reported to be increased in schizophrenic patients. These EPs recorded above the somato-sensory cortices were very early [199, 201] and the methods could hardly be compared.

Evoked gamma activity driven by 40 Hz auditory or visual stimulation has been shown to be attenuated in schizophrenic patients [182, 189, 215-217]. Early evoked responses to auditory or visual task stimuli have not consistently differed between patients and controls. Some reports show attenuated evoked gamma activity at 50-200 ms latency [188, 213, 214] and others show early evoked activity to be unaffected by diagnosis [106, 183, 185].

The facts that the general left hemisphere gamma activity was reduced in the schizotypal patients and the specific onset activity in the left hemisphere in the predictable condition was reduced in both patient groups, could be a consequence of the complexity of gamma modulation. General arousal and more specific attentional modulation seem to concur. For that reason, the findings lend less strong support to the idea of an proprioceptive gamma dysfunction derived from the proposition by Sandor Rado [4, 218].

The presently observed attenuation of evoked contra-lateral beta activity in the patients was noteworthy temporal and regional specific. The slightly later evoked frontal beta activity at lower frequencies was not attenuated. The circumscribed contra-

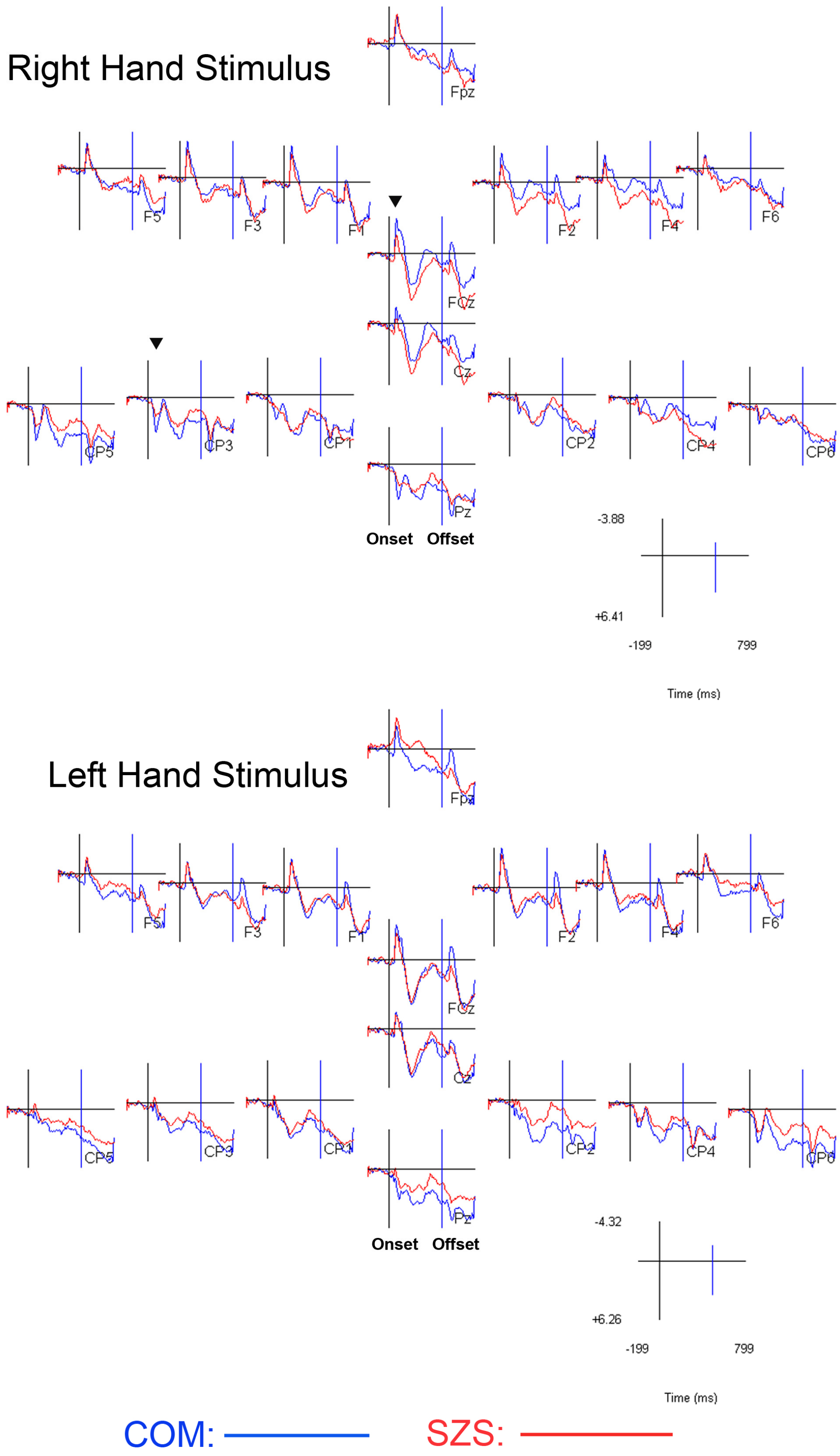


Figure13 Multi channel proprioceptive ERPs in healthy subjects and schizophrenia spectrum patients.
Grand averages for each subject group and hand of stimulation. Comparing SZS: patients with schizophrenia spectrum disorder (N=18), red line, with COM: healthy comparison subjects (N=18), blue line in the Regular condition. Black vertical line marks onset (time 0 ms) and blue vertical line marks offset (time 500 ms) of the proprioceptive stimulus. Arrows mark the peaks where the avWT analyses yielded significant group differences. Please note that the y-axes are not identical in the two sides.

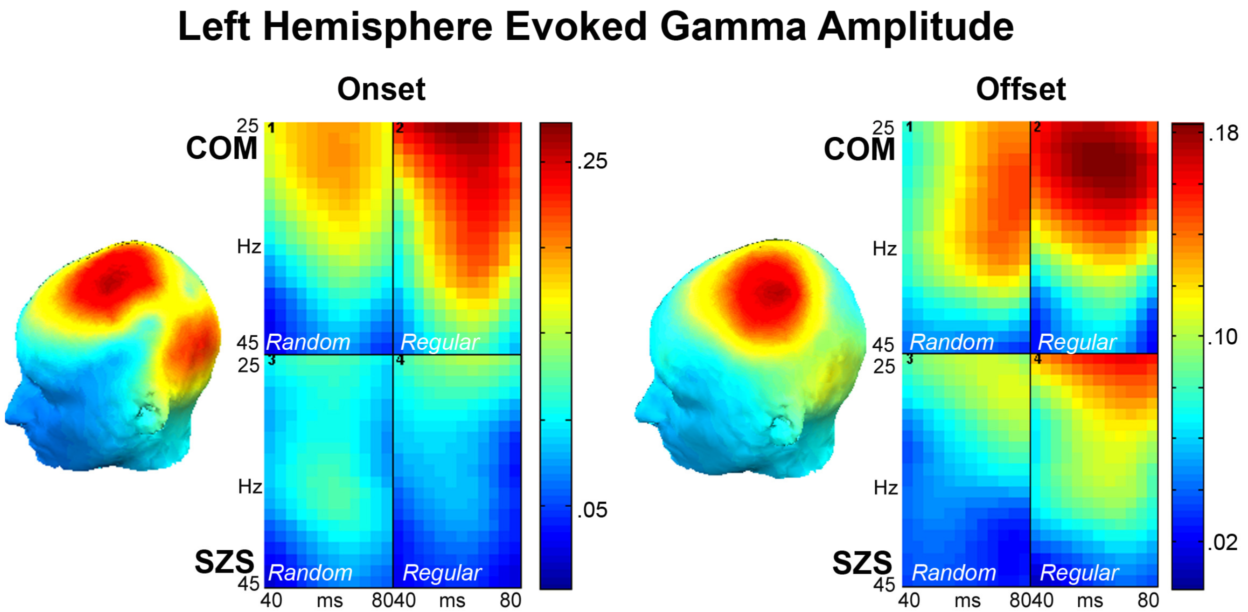


Figure 14. Schizophrenia spectrum patients demonstrate attenuated proprioceptive evoked gamma oscillations in the left hemisphere
A grand average display of the non-negative matrix analyses of right hand stimulus evoked gamma activity (WOI: latency 40-80 ms; frequency 25-45 Hz, contra-lateral (left hemisphere) electrodes)). The collapsed data of the comparison subjects (18 (subjects) x 108 epochs = 1944 epochs) (COM) and the schizophrenia spectrum patients (1944 epochs) (SZS) in the Random and Regular condition were included separately in the analyses, thereby creating separate time-frequency plots for each group and condition, while the head plots at the left side show the common topography. The observable overall group difference is significant as is the specific difference between COM and SZS in the Regular condition at onset. Please note the difference in scaling in the colour bar for onset and offset.

lateral attenuation of beta oscillations in the patients could be an effect of specific deficiencies in the generation of higher frequencies (16 Hz vs. 21 Hz) or it could be an effect of less priming by the experimental set i.e. the continuous hand posture.

In this manner the results could support the hypothesis of a deficiency of corollary discharge in schizophrenia [13, 14]: In a situation of voluntary isometric contraction as in this task of a light grip of the hand, the corollary discharge signal preparing the sensory cortices for the feedback input would inhibit sustained expected sensory feedback and facilitate processing of input from an external perturbation i.e. the patients would be expected to have less beta facilitation.

Yet, it would not be possible to determine whether the diminished beta activity observed across hand and stimulus sequence was due to lack of facilitation or due to a focal parietal dysfunction. Beta activity is less explored in schizophrenia than gamma, and the findings are inconsistent. Phasic beta activity has only been examined in a few studies of schizophrenic patients, reporting no difference in pre-movement beta ITPC [205] but increased beta pre- and post-stimulus amplitudes in schizophrenic patients in the auditory paired-click paradigm [183].

The chronic patients showed no proprioceptive gating deficits (III) and the lack of difference between the healthy subjects and schizophrenia patients in response to onset and offset of the propriceptive stimulation in (VII) also indicated that the investigated patients had a normal repetition inhibition in the proprioceptive modality. This is in accordance with some previous findings in the somatosensory modality [2, 219], but not all [220]. The latter magnetencephalographic study could report a gating deficiency localized to secondary somatosensory cortices at around 80 ms latency [220]. These patients were older and had a longer duration of illness as well as much more severe negative symptoms, than the patient samples included here.

6. MAIN CONCLUSION AND CONSTRAINTS

A new load stimulus was constructed. This load stimulus evoked consistent contra-lateral cortical activity (I-III, V-VII) which has been named the proprioceptive EP. Furthermore, the stimulus evoked contra-lateral early gamma activity which previously had only been observed in the somatosensory modality following electrical stimulation (V-VII). Load discrimination was more difficult than expected and the mechanical properties of the device induced some limitations in its applications, but the stimulus was easy to apply in different contexts and easy to tolerate for the investigated subjects.

The load stimulus was applied in different types of stimulus paradigms that uncovered modulations by repetition and attention. The later potential components were modulated in the same way as otherwise observed for somatosensory event related potentials. A new paradigm of regular vs. random hand of presentation was designed aimed at testing the effect of predictability on the early proprioceptive evoked activity. In the first study of healthy subjects, predictability affected high frequency parietal beta activity, while gamma, alpha and lower frequency beta activity was unaffected (VI). This effect was not seen in the subsequent clinical study, where much fewer trials were obtained. Effects of ISI and temporal predictability confounded the results, and precaution is necessary in the interpretation of the findings as result of cortical priming.

Detailed mapping of the proprioceptive EP were achieved through progress within factor analysis algorithms. The new analyses were validated against previous research findings and against visual inspection of data and the findings substantiated that non-negative matrix analysis could be applied both for exploratory and confirmatory analyses, although the analysis required substantial data pre-processing and narrow windows of interest. Applying the non-negative matrix analysis, early proprioceptive activity was decomposed into three or five time-frequency components depending on the frequency range investigated (VI, VII).

In accordance with the main study hypothesis and with the suggestions by Sandor Rado, schizophrenic patients demonstrated subtle, though significant, abnormalities of proprioceptive information processing, when examined with the new load stimulus (III, VII). The finding of left hemisphere attenuated early gamma activity in schizophrenia spectrum patients (VII) is the first report of somatosensory evoked gamma activity in schizophrenia.

The left contra-lateral parietal cortical activity 60-120 ms following the load stimulus was affected in two different experiments and in two different samples of schizophrenia spectrum patients (III, VII). In the first experiment a delay was observed and in the second experiment diminished amplitude and precision of high frequency activity. In the second experiment the schizotypal patients were more affected than the schizophrenic patients, who had a specific attenuation of gamma activity at the onset of the load stimulus in the predictable sequence (VII).

Considering previous research on somatosensory activity in this latency range, the results could be understood as diminished priming of left hemisphere somatosensory cortex in a situation of posture maintenance and expectation of perturbation (III, VII). This interpretation would be in accordance with the theory of deficiency of corollary discharge or the theory of weakening of the influence of past regularities in schizophrenia [11-14]. No abnormality of gating was observed (III, VII) and the imprecision and amplitude attenuation was not a general phenomenon across the entire brain response. This rebuts the theory of general cortico-cortical dys-connectivity [87-91].

No evidence supports a causal relationship between abnormal proprioceptive information processing and symptoms of schizophrenia, but this might be due to the heterogeneity of each of the patients groups (III, VII) and the small sample sizes. The first sample consisted of un-medicated male patients across a large age span, some chronic and some that newly had fallen ill, while the second was medicated mixed gender patients in their first admission and the majority was not psychotic. Generally the level of symptoms was low and this might explain the fact that the abnormal cortical activation was uncorrelated to psychopathological ratings. Arousal level was not measured, which was regrettably as recent research have implied important modulation of early sensory gamma activity by arousal [204] and schizophrenia spectrum patients are known to have divergent abnormalities of arousal level [197].

Another issue in need of further investigation is the relationship between cortical activation and load perception, which was only indirectly measured (II).

Returning to the very first question posed: “What could be the brain substance of these bodily sensations?” the ultimate answer is not achieved. Speculatively, lower precision of the early cortical response in the sensory-motor cortex could induce diminished recognition of movements and postural muscular tensions as self-generated and thereby promote delusions of control and attenuate the development of a sense of self.

The latter could be basic to the observed self-disorder in the patients [190, 192, 221]. The sense of self relies on the establishment of sensory-motor equivalencies and on perceptual integration [222] and efficient sensory-motor operations is considered basic to the developmental formation of perceptions, conceptual objects and the creation of cognitive schemes [223]. If lower precision of the early cortical response in the sensory-motor cortex could be confirmed in children later to develop schizophrenic symptoms, this trail of thought would be less speculative.

Directions for future clinical work

Investigations of core deficiencies in schizophrenia are complicated by the fact that anti-psychotics and acute psychosis have major effects on brain activity. Un-medicated patients in a stable condition are necessary for future substantiation of the present findings. The investigation of the link between proprioceptive information processing and specific trait-like symptoms might be optimally conducted in non-clinical schizotypal patients avoiding confounding effects of acute illness and medicine.

Further experiments on load discrimination, spatial attention and a phenomenological examination of the perceptual experience in healthy subjects could establish the link between cortical activity, and proprioceptive perception, which subsequently could spur more specific hypotheses about the link between imprecision in somatosensory cortical activation and symptoms in schizophrenia.

Investigations of gamma activity following stimuli of several modalities in comparable paradigms in the same patient sample could map supra-modal deficiencies more precisely and confounders like the level of arousal should be examined.

SUMMARY

This doctoral thesis focuses on brain activity in response to proprioceptive stimulation in schizophrenia. The works encompass methodological developments substantiated by investigations of healthy volunteers and two clinical studies of schizophrenia spectrum patients.

American psychiatrist Sandor Rado (1890-1972) suggested that one of two un-reducible deficits in schizophrenia was a disorder of proprioception. Exploration of proprioceptive information processing is possible through the measurement of evoked and event related potentials. Event related EEG can be analyzed as conventional time-series averages or as oscillatory averages transformed into the frequency domain. Gamma activity evoked by electricity or by another type of somatosensory stimulus has not been reported before in schizophrenia. Gamma activity is considered to be a manifestation of perceptual integration.

A new load stimulus was constructed that stimulated the proprioceptive dimension of recognition of applied force. This load stimulus was tested both in simple and several types of more complex stimulus paradigms, with and without tasks, in total in 66 healthy volunteers. The evoked potential (EP) resulting from the load stimulus was named the proprioceptive EP. The later components of the proprioceptive EP (> 150 ms) were modulated similarly to previously reported electrical somatosensory EPs by repetition and cognitive task. The earlier activity was further investigated through decomposition of the time-frequency transformed data by a new non-negative matrix analysis, and previous research and visual inspection validated these results.

Several time-frequency components emerged in the proprioceptive EP. The contra-lateral parietal gamma component (60-70 ms; 30-41 Hz) had not previously been described in the somato-

sensory modality without electrical stimulation. The parietal beta component (87-103 ms; 19-22 Hz) was increased when the proprioceptive stimulus appeared in a predictable sequence in several runs of recording. Although the experimental paradigm had inherent confounders, it was suggested that the increase observed in the predictable situation, in healthy subjects, was due to priming of the somatosensory cortex through top-down modulation.

The proprioceptive EP was investigated in two different samples of a total of 30 schizophrenia spectrum patients. The left contra-lateral parietal cortical activity 60-120 ms following the load stimulus was affected in both samples. In the first experiment a delay was observed and in the second experiment diminished amplitude and trial-to-trial phase consistency of high frequency (18-45 Hz) activity. Both effects were interpreted as a consequence of diminished precision of activation of the left somatosensory cortex and it was suggested to be in accordance with two theories of schizophrenic information processing: the theory of deficiency of corollary discharge and the theory of weakening of the influence of past regularities. No gating deficiency was observed and the imprecision and amplitude attenuation was not a general phenomenon across the entire brain response.

Summing up, in support of Rado's hypothesis, schizophrenia spectrum patients demonstrated abnormalities in proprioceptive information processing. Future work needs to extend the findings in larger un-medicated, non-chronic, patient samples and investigate the connection between schizophrenic symptoms, perception and attenuation of the proprioceptive EP.

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