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Bereitschaftspotentials as a Tool to Study Motor Neuroscience

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Abstract: ***The year 2016marks the 52th anniversary tothe discovery of bereitschaftspotentials by Kornhuber and Deecke.Using a unique opisthochronic averaging technique, the discoverers found a consistent negative cortical potential that developed about 1500 to 1000 milliseconds prior to the onset of a self-paced movement. For the first time, it was possible for the scientific world to study the activity of the brain prior to an actual onset of movement. Their discovery changed the outlook of scientific world towards human brain from a passive reflexive organ to an active planner. Ever since this technique has opened new doors to unravel the secrets of motor physiology of the human brain. In this review article, we discuss in details the use of the bereitschaftspotentials to understand the temporal pattern of cortical activity prior to movement in health and in disease, including the study of brain areas and factors influencing motor planning and execution.***

Keywords: bereitschaftspotentials, motor planning, supplementary motor area, basal ganglia, cerebellum

1. Introduction: Concept, Terminology and Components

Bereitschaftspotentials (BP) represent the cortical activity that comprises the planning and execution phase before the actual onset of movement (2). The name of these potentials derives from a German word "bereitschafts potentials" literally meaning readiness potentials. Indeed, BP is an event-related potential that is locked to the onset of movement or electromyography. Thus, BP can be considered as a motor-related cortical potential (MRCP), but there is wide consensus not to use these two terms interchangeably. The MRCPs include both the pre-movement as well as the post-movement related cortical potentials (3); and the term bereitschaftspotential is to be restricted to former. The large amplitudes of BP from scalp recordings suggest that these potentials represent the summated activity of the postsynaptic potentials arising from apical dendrites of the cortex(4). The slow negative potential found in BP represents the excitability rather than the absence of facilitation of the underlying cortical tissue, and such a cortical excitability is regulated by feedback loops arising from the subcortical structures especially the basal ganglia(5). Interestingly, the bereitschaftspotentials can be recordedprior to voluntary movements of any part of the body like hand, fingers, leg, tongue, pharyngeal muscles (swallowing), eye movements(6–10).Thus, these cortical potentials can be viewed as the fundamental principle in motor physiology that applies to all voluntary motor actions. A vast number of experiments have identified that the waveform of BP has multiple components (Figure 1).This is evident by the change in slope observed in the BP waveform with time orby comparing the BP waveform in patients with neurodegenerative diseases or lesions. Broadly, the BP is subdivided into two components (11). The early component of BP is the first negative slope of BP that starts about -1500 milliseconds prior to movement onset (i.e. at the onset of bereitschaftspotentials) and lasts up to -500 milliseconds as the slope of the potential change at around this time(2,11). While the late BP consists of rapidly increasing second negative slope that begins -500 milliseconds prior to movement(2,11).Many past studies have referred to these components with various names like BP, RP, NS, etc. creating confusion for referral in future studies but as described in the original description the nomenclature should be standardized for the early component as early BP or BP1 and for the late component as late BP or BP2(1,11).Another third component of BP that begins about -60 milliseconds prior to movement onset represents the activity of the contralateral cortex is MP (Motor Potential) or Peak BP (12).

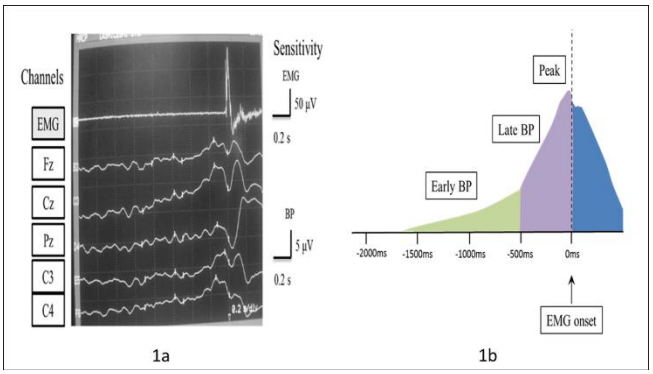

Figure 1: (a) shows a typical record of BP at various scalp sites according to 10-20 electrode placement system along with EMG response at the top. This graph represents an average response of 100 artifacts free trials recorded prior to self-paced wrist extension with EMG from extensor carpi radialis used for back averaging EEG signal. Note the waveform at site Cz shows the maximum amplitude. (b) This is a schematic diagram of BP; note the different components of BP relative to EMG onset. (111)

2. BP recording technique and analysis

Bereitschaftspotentials can be recorded for any voluntary motor activity. The trigger for the averaging the electroencephalography (EEG) can be an electromyograph (EMG) or movement onset; though using an electric event would be more specific. The volunteer is usually asked to repeat the movement once for every 10-20 seconds. Interval

time less than 5 seconds tend to give smaller duration on BP and overlapping records. The EEG record during rest (between the trials or 6 seconds before movement) is used to obtain the baseline for BP parameter calculations. Artifact removal before averaging the data is as important step to get a clean data. Simultaneous recording of EOG (electrooculography) and EMG from neck muscles is used to remove such disturbances and along with visual inspection must be performed to remove any shift in EEG record or potentials larger than 100 microvolts. Averaging of at least 100 or more artefacts free EEG records 5 seconds prior to and 2 seconds after the EMG is adequate to get a good BP record.

Onset times of the potential is the first parameter to be noted (109). Complex or sequential tasks tend to have onset times must more prior to movement than simple motor tasks. Intend of movement and even training affects the onset times. An earlier onset time necessarily indicates more preparedness by the cortex. Many parameters are used to analyze the various components of BP. From the onset of BP or -1.5 seconds prior to movement onset to -0.5 seconds prior to movement is the duration of early component (2). Average/maximum amplitude, slope as calculated by linear regression, or area during this duration have been used as parameters to quantify early BP (54,106,110). About -0.6 to -0.5 seconds prior to movement the slope of BP increases this marks the start of late component. Similar to early BP; average/maximum amplitude, slope, and area have also been used for late BP (54,106,110). Peak amplitude of BP generally occurs -0.05 seconds prior to movement is Peak BP or motor potential (12). Also post-peak slope change and topography of BP are measures used to compare within the subjects (46,72). It is worthwhile to note that intrasubject variability is low for late BP, Peak BP and even for amplitude at 0 seconds (110). A method to increase power of the study is to generate lab specific control data (age and gender matched) for comparison between disease groups. The peak time and amplitude after movement form other subsets of parameters of post-movement potentials.

Bereitschaftspotentials can be recorded from the scalp as well as directly from the cortex (13,14) Direct intra-cerebral recordings demonstrate BP over the bilateral supplementary cortex and the contralateral primary motor cortex (15). These potentials can also be recorded from sub-cortical areas like thalamus (16), subthalamic nucleus (17), pedunculopontine nucleus (18), caudate (19), putamen (19), pallidum (19).The polarity of BP recorded subcortically is reverse of that recorded at scalp implying the generator sources of these potentials in the cortices. Though doubted, the subcortical BP recordings do not necessary mean volume conduction from cortical regions; as lesions in these subcortical structures do produce a reduction in amplitudes or waveform abnormalities in BP (20). Apart from this, lesion or degeneration of other motor-related brain regions like the prefrontal cortex or cerebellum also affects the BP (21,22). Thus, an intricate network of cortical and subcortical areas is important in modulating the motor cortices and in the generation of BP. The study of bereitschaftspotentials provides us with an easy method to understand motor physiology in health and in disease.

3. Bereitschaftspotentials as a tool to study Motor Neuroscience

Neurophysiological recording of potentials prior to and after movement helps in understanding the temporal sequence of activation of various cortical areas involved in movement. The higher temporal resolution of movement related cortical potentials provides an excellent research tool to understand motor physiology(23). Voluntary activity precedes by bilaterally activation of supplementary cortex (pre as well as proper SMA) followed by contralateral activation of premotor area and primary motor cortex (24). The location of BP and their topographical differences during finger and toe movement imply the role of both supplementary as well contralateral primary motor cortex in genesis of BP(25).We discuss below the contribution of BP in understanding the role various motor related brain areas prior to and during motor activity.

Supplementary motor area: Supplementary motor area (SMA) plays an essential role prior to voluntary movement during the preparation phase. It organizes, co-ordinates, and plans the order of movement (26–31). One of the commonest use of measuring bereitschaftspotentials is to study the activity of the supplementary motor cortex as suggested by the discovers of these potentials (1,2). The study of these potentials have helped in exploringthe role of supplementary cortex prior to and during movement. Topographical organization of the BP recorded prior to finger or toe movement show that it is maximum at the vertex, just above the location of supplementary motor area (25). Onset of BP is earliest over supplementary motor cortex in both simple as well as complex writing tasks (32); this in fact suggests the fundamental role of SMA in motor planning.Amplitude of BP is more for complex motor tasks involving simultaneous or sequential movements than simple motor tasks (33)and is restricted to the vertex (Cz) (34) which reflects increased activation of SMA with increasing complexity. At times supplementary motor area is more active than primary motor cortex when tasks are demanding and complex (35) and alongside the onset of BP is earlier in complex tasks (32). Even neurophysiological studies using single unit recording technique demonstrate activity in the neurons of bilateral supplementary motor cortex before movement. The firing patterns of these neurons is of two types; some start firing almost 2 seconds before movement while others have short lead times (36). No wonder the cortical potentials can be recorded over this part of cortex. Direct recording from the supplementary cortex with the use of subdural electrodes has shown that BP is somatotopically distributed in SMA-proper while a region anterior to SMA-proper, supplementary negative motor area had BP recordings independent of movement site (37). SMA-proper is the caudal part of supplementary motor area and like primary motor cortex has directs projections to the motor neurons in the cervical and lumbosacral regions (38,39). Stimulation study showed somatotopic organization in human supplementary motor cortex and most projections to spinal motor neurons are from contralateral SMA (40). While, the rostral part or supplementary negative area appears to play a general role in motor planning of all body parts. Thus differential functions are assigned to the caudal and the rostral parts of SMA during motor preparation and

execution with former involved primarily during execution while latter during preparation (41). Among all the subcortical areas, the supplementary motor cortex receives extensive inputs from the output nuclei of basal ganglia(42). Imaging studies have found decreased activation of SMA prior to movement during basal ganglia dysfunction (Parkinson's disease)(43). The decrease in amplitude of early part of BP in Parkinson's disease (PD) is in fact due to SMA under-activation(44–46). The reduction in BP amplitude correlates with the severity of Parkinson's disease rather than the duration(47). The reduced early component of BP is increased to recordable level in de novo patients of PD after levodopa administration (48). Levodopa increases the activation of SMA prior to movement in the disease (49). Again justifying the result that the reduced activation of supplementary motor cortex by pallido-thalamo-cortical projections due to dopaminergic loss in PD is the reason for reduced BP amplitude in the disease(47). Lesions of SMA have shown that the topography of the potentials is affected globally with reduction in the amplitude of BP at vertex and contralateral SMA contribute more to BP generation than ipsilateral (50). Deecke et al discovered of an another potential called pre-motion positivity (PMP)(51). This PMP starts after the late BP but before motor potential and is bilaterally symmetrical; probably an index for movement initiation(51,52).The generator source for PMP is SMA (53); which also justifies the role of SMA in movement initiation.

Primary motor cortex: Voluntary movements are preceded by activation of contralateral primary motor cortex. The activity contributed by contralateral motor cortex in BP starts after the bilateral activity of SMA (54). The late BP and peak BP (motor potentials) have their genesis sources principally from the contralateral motor cortex (11,12,55,56). Increasing surface negativity (Motor potential/ Peak BP) is found about 56 milliseconds before onset of movement which is maximum over the contralateral precentral area (51). Motor potentials have even been recorded directly from the hand area of contralateral primary motor cortex in humans undergoing epilepsy surgery(57). Recording of BP using subdural electrodes is very useful tool to functional map the contralateral motor area during surgeries like epileptogenic resection and tumors (58). Another use of BP is to study the difference in motor cortical activity during actual movement versus imagination. Late component of BP is same on both sides of the scalp during imaginary motor task (54); as there is no lateralization of activity during imagination the role of primary motor cortex is minimal during such situations. While, the execution related component found when BP recorded during actual movement is subtracted from imaginary task is lateralized over the contralateral primary motor cortex (54). However, neuronal recordings in primate study do demonstrate activity of primary motor cortical neurons during anticipation in a sequential motor task (59); implying an important role of motor cortex prior to sequential tasks. Indeed a human TMS study has shown that the primary motor cortex activity is more for complex tasks than simple (60).The exact contribution of primary motor cortex and supplementary motor area during imagination of sequential motor task is yet to be explored. BP can be used to evaluate insufficiencies or deficiencies in activation of contralateral motor cortex during movement in diseases like writer's cramp where these patients show decrease in amplitude of BP over contralateral sides (61).

Basal ganglia: Basal ganglia consist of multiple segregated circuits including motor, occulomotor, associative and limbic circuits (62).The motor circuit is implicated in pathophysiology of both hypokinetic and hyperkinetic movement disorders (63). Abnormal basal ganglia activity due to dopamine depletion results in delay in preparatory activity within SMA and changes in BP (64). Both early and late components of BP is reduced in lesions to basal ganglia with unilateral lesions in basal ganglia reducing the BP on the impaired side (20). Certainly, the feedback loops from basal ganglia to motor cortices have an important role in genesis of BP. Taking the advantage of electrodes implanted during various surgeries; BP has been recorded in various nuclei of basal ganglia. The input nuclei of basal ganglia, caudate and putamen, receive extensive glutaminergic input from the cortex (65). Such input is somatotopically organized with contribution both from SMA and primary motor cortex neurons and such a somatotopy is followed throughout all the basal ganglia nuclei-thalamus and back again to the cortex (66). During epilepsy surgery, Rektor et al., demonstrated recording of BP simultaneously from motor cortex, caudate, putamen, and pallidum. The BP were recorded in contralateral caudate and putamen and had onset latencies slightly late than those recorded over cortex (19). Paradiso *et al.* recorded movement potentials using electrodes implanted from subthalamic nucleus. Movement related potentials were observed in subthalamic nucleus prior to both unilateral as well as bilateral movement and had same latencies as that of scalp recorded BP (17). The already known information about subthalamic neurons having direct input from motor cortex (67) plus having increased firing pattern associated with movement (68) and the finding of recordable BP in subthalamic nucleus has helped in establishing the role of STN in movement preparation (17).

Cerebellum: Cerebellum does play a role in motor planning as evident by recording of movement related potentials prior to voluntary contractions in the ventro lateral part of thalamus which predominantly receives inputs from dentate nucleus (16). The reduced late BP in patients of essential tremors may in turn be contributed by dysfunctional cerebellodentate-thalamo-cortical pathway (69). Cerebellar degeneration also leads to abnormal topography of BP prior to movement with loss of contralateral dominance of initial slope of Peak BP or MP and also shift frontal peak MP (fpMP) more posterior than in normal individuals (70). Lesions in efferent pathways of cerebellum affects BP suggesting the role of cerebellum in genesis of BP(71). Peak BP amplitude is reduced and topographic maximum over Cz site is changed in location in cebellar atrophy patients during goal directed self-paced motor task; this definitely suggests the role of cerebellar inputs to cerebral cortex in genesis of BP (72).

Prefrontal Cortex& Premotor cortex: Though study using subdural electrodes has failed to record BP over prefrontal cortex(73); lesions in prefrontal cortex results in reduction in BP prior movement (22) and reduction in later component of CNV (74). This late component of CNV shows striking

relations to BP as in varying similarly with subjective factors and speed as well as having almost similar topography (75). Patients suffering from prefrontal cortex lesions have differential effect on early and late components of BP; implying role of prefrontal cortex in motor planning (22). Along with SMA, premotor cortex may also play a role in volitional movement and in genesis of BP (44,76). The exact nature of how prefrontal cortex and premotor area influence motor physiology as reflected in BP is yet unclear. These areas may play a role while studying the effect of various factors on BP.

4. Factors affecting Bereitschaftspotentials

Recording the cortical activity in the form of motor related cortical potentials may be used as a tool to understand the supraspinal influences on motor activity (93).

Actual or imagined tasks: Amplitude of BP is more when actual self-paced movement is performed rather just planning the task (94). Also amplitude of BP is more when the task is performed versus imagining or watching the motor task (46). Both early and late component of BP are larger during actual movement tasks than imagined ones (95). Early component of BP is recorded not only during actual movement but also during imaging the movement (54). Late component of BP was found to be the same on both sides of the scalp during imaginary motor task (54); as there is no lateralization of activity during imagination the role of primary motor cortex is minimal during such situations. The presence of the BP prior to imaginary movement can be used as an efficient predictor in brain computer communications in paralysis (96).

Training: Resistant training exercises decrease the amplitude of BP and result in earlier onset times (93). Reduction is seen in motor potential after 3 week resistant training exercise regime; this would necessary mean that there less activation of motor cortex required to perform the same task as less motor units need to be recruited (93). Earlier onset times and reduced amplitude of BP is also seen in elite rifle shooters compared to controls suggesting better and efficient planning of motor actions in elite group (97). Motor related potentials start late and have smaller amplitude in athletes than controls and this might be due specific or economic use of motor neural circuits by the former group especially when time to do motor activity is crucial (97,98). Recording BP can be used clinically as an exercise guide in Parkinson's disease and can additionally provide a neuro-feedback to the patient to monitor his/her progress. Such a technique has already shown to increase early BP amplitude subsequent to training in healthy individuals (99).

Force, Intend and Fatigue: The amplitude of BP correlates positively with the force and rate of force of contraction (100–102). Larger amplitude in early and late component of BP is observed during high torque than low torque actual or imagined plantar flexion tasks in healthy subjects (95). BP amplitude is more during forceful and fatiguing contractions than less forceful non-fatiguing ones (100). Precise contractions at lesser force produced increase in BP implying the role of more motor cortical involvement in such situations (100). Factors like force of contraction, rate of force development, fatiguing contractions, and types of actions affected the magnitude of BP (103). The amplitude of BP is dependent on the level of involvement of the subject in the motor task as boredom or repeated stereotypic automated motor tasks result in smaller BP (1,104). Amplitude of BP is reduced if the movement is auto triggered with painful shock; such an observation points toward the important of intention or state of preparedness in genesis of BP and this may also denote that individual has ability to suppress the cortical activity in anticipation of pain (105). The amplitude of late component of BP is larger when individuals are asked to do freely selected joystick movements than fixed direction movements (106).High time pressure to solve arithmetic tasks leads to increase in amplitude of BP prior to movement (107). BP does not differ whether the agonist or antagonist muscles are used; neither does it differ between simultaneous or sequential movements of finger (108).

5. Bereitschaftspotentials in disorders

The potentials have been widely studied in various motor disorders, particularly the Parkinson's disease. The degeneration of dopaminergic neurons in Parkinson's disease alters the output of basal ganglia leading to prominent motor and non-motor symptoms in the disease. Some of the studies have shown near normal BP in Parkinson's disease compared to age matched controls (77,78); however many other studies have found abnormalities in the potentials (20,44,46,47,54,79,80). There is reduction in amplitude of BP throughout the waveform development in bilateral and unilateral Parkinson's disease(47). Dopaminergic medications can improve the reduced peak amplitude of BP in healthy individuals as well as in patients suffering from Parkinson's disease (48,81). Amplitude or slope of early BP as well as peak amplitude is lower in patients with PD compared to controls during self-initiated movement task (44–46), but not for externally triggered tasks (44), thus the patients compensate for movement initiation by relying more on external cues during motor tasks (82). Advanced stages of the disease is associated with reduced slope of BP as compared to early stages in PD (54) and reduction in BP amplitude correlates with the severity of Parkinson's disease rather than the duration (47). The BP waveforms are completely abolished after unilateral thalamotomy (intermedioventral part) in PD (21); thus the basal ganglia output via this region in thalamus plays an important role in BP genesis. While, posteroventral pallidotomy improves the late component of BP in Parkinson's disease and thus improves the motor execution phase in these patients while levodopa improves the early component and increasing the supplementary motor cortex activity (83). BP abnormalities found in the Parkinson's disease are reversed back to some extend using levodopa, but it is still unclear whether newer treatment modalities like deep brain stimulation or newer medications also modulate the BP waveform and thus the motor planning phase of movement.

Amplitude of BP is decreased in idiopathic torsion dystonia and there is no lateralization of late component of these potentials in the disease (84). Lateralization of BP to the

contralateral motor cortex is also absent in patients with persistent mirror movements (85). While the former disease dystonia, represents a dysfunction in basal ganglia leading to abnormal brain motor networks and the symptoms (86); the latter persistent mirror movement disorder may be due to abnormal cross talk between the two motor cortices via corpus callosum (87,88).Yet in both disorders, the lateralization of BP to the contralateral cortex is affected. Most of the diseases result in decrease in BP amplitude, but BP amplitude is significantly more in schizophrenic patients with tardive dyskinesia than controls or schizophrenics without dyskinesia (89). While psychiatric disorders like schizophrenia show BP abnormalities; the potentials are normal in children with bipolar disorders (90). BP is absent prior to involuntary jerks in myoclonus; present in some of the jerks in Gilles de la Tourette syndrome with smaller waves and increased in patients with psychogenic jerks(91). Presence of BP prior to psychogenic jerks can thus be used to aid in its diagnosis differentiating from other jerky movements (91,92).

6. Conclusion

Human brain learns to plan earlier for complex or sequential tasks (like archery) and at times,it learns to delay the planning for quick and automated responses (required by sprint athletes) as reflected by onset latencies of BP. Indeed the study of bereitschaftspotentials has been a good temporal evaluator to cortical activity prior to movement. Bilateral SMA preferentially contributes the early part of BP and while contralateral primary motor cortex contributes to the late part of BP with somatotopic activity in SMA-proper and M1. The potentials are influenced by intricate neuronal circuitry from basal ganglia and cerebellum via thalamus, and probably directly from prefrontal and parietal areas onto the SMA. Diseases affecting any parts of this system thus reflects in abnormalities in BP waveform. Future studies can be directed towards modelling of these circuits using characteristics of BP waveform as training parameters to better understand motor planning in health and disease.

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