Spectral Analysis of Field Potential Recordings by Deep Brain Stimulation Electrode for Localization of Subthalamic Nucleus in Patients with Parkinson's Disease

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TITLE

Spectral analysis of field potential recordings by DBS electrode for localization of subthalamic nucleus in patients with Parkinson's disease.

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Short title

Subthalamic field potential by DBS lead

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KEY WORDS
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ABSTRACT

Aims: The spectral analysis of local field potential (LFP) recorded by deep brain stimulation (DBS) electrode around the subthalamic nucleus (STN) in patients with Parkinson's disease was performed. ***Methods:*** The borders of STN were determined by microelectrode recording (MER). The most eligible trajectory for sensorimotor area of STN was used for LFP recording while advancing the DBS electrode. ***Results:*** The low-frequency LFP power (θ- to β-band) increased from a few mm above the dorsal border of STN defined by MER; however, the low-frequency power kept the same level beyond the ventral border of STN. Only high β-power showed the close correlation to the dorsal and ventral borders of STN. ***Conclusions:*** A spectral power analysis of LFP recording by DBS electrode helps with the final confirmation of the dorsal and ventral borders of STN of Parkinson's disease in DBS implantation surgery.

INTRODUCTION

In Parkinson's disease (PD), it is postulated that dopamine depletion in the striatum leads to an oscillatory synchrony in low-frequency (β-band) neuronal discharges of the basal ganglia [11]. Such oscillatory synchrony is considered to induce the antikinetic effect on the interaction between the motor cortex and basal ganglia in the "off" state of PD, but when the patient's motor function is turned to the "on" state by levodopa treatment, the β-band oscillation disappears or changes into γ-band oscillation [2].

In some studies on local field potential (LFP) in the basal ganglia, a low impedance microelectrode was used during stereotactic neurosurgery [10,18,19]. However, the LFPs can be recorded using deep brain stimulation (DBS) electrode during surgery [3,5,13] or during the trial period after implantation using an externalized cable [5,7]. Chen et al. reported that the subthalamic nucleus (STN) can be physiologically localized by DBS electrode alone, without performing microelectrode recording (MER) [3]. In their study a DBS electrode was inserted by a 2-mm step. When the contact got into STN, the spectral change was observed; however, the details of the border of the STN was not identifiable with the 2-mm step insertion. Since the depth of dorsal and ventral borders defines the physiological width of the STN, which is considered a major determinant of the eligible trajectory for implantation of a DBS electrode [16,17], the detailed characteristics of LFP around the dorsal and ventral borders provide crucial information if MER is not performed. The purpose of this study is to characterize the LFP changes around the STN borders, and to identify the dorsal and ventral STN border by the change in LFP from the DBS electrode.

MATERIALS AND METHODS

Patients

Nine STNs from 7 patients with idiopathic PD (2 males and 5 females, with a mean age of 65±5.3 years ranging from 50 to 71) were included for the LFP recording during DBS surgery. All patients had disabling motor fluctuations and/or levodopa-induced dyskinesia refractory to the adjustment of antiparkinsonian medication. The mean disease duration was 14±8.5 years, and the mean Hoehn-Yahr stage was

3.9±1.1 in the "off" state and 2.7±0.8 in the "on" state. The patients were treated with levodopa and dopamine agonists; the daily dose of levodopa was 586±306 mg/day (total levodopa equivalent dose 884±458 mg/day). In five patients, only unilateral STN was explored for LFP recording because of limited operation time.

Surgical Procedure

All patients gave their informed consent for DBS implantation surgery and related data acquisition. Surgeries were performed in the "off" state after an 18-hour discontinuation of antiparkinsonian medication. After a stereotactic head frame (Leksell model G, Elekta) was affixed to the patient's head under local anesthesia, the patient underwent preoperative magnetic resonance (MR) imaging and helical computerized tomography (CT). The axial images were transferred to the workstation computer in the operating room in a DICOM format. The data were imported into the computer soft software, SurgiPlan™ (Elekta, Sweden). After both 3D images reconstructed from MR and CT were exactly matched, as confirmed by the image fusion tool, the coordinates of the anterior and posterior commissures (AC and PC) were directly calculated by the software. The theoretical target was placed 11-12mm lateral to the AC-PC line, 3mm posterior and 5mm ventral to the midcommissural point. The laterality of the theoretical target from the AC−PC line was also individually modified, as 3mm lateral to the lateral border of red nucleus visualized on T2-weighted coronal image in each case. The coordinates were also calculated separately by manual drawing on the X-ray film, and a consensus was obtained with the results from the "functional target" tool of SurgiPlan™. The entry point (site of burr hole) was placed around the coronal suture and 3-4 cm lateral to the midline; the final trajectory was planned to avoid the cortical sulci and lateral ventricle. The patient's head with head frame was secured to the operative table, and the patient was postured in a supine position to prevent a brain shift during the burr-hole surgery [15].

Multi-track Microrecording

A semicircular skin incision and burr hole was made at the entry point. Immediately after the dura mater was opened, the burr hole was covered with fibrin glue to prevent the outflow of cerebrospinal fluid during surgery. Four cannulae for multi-track microelectrode recording (Array electrode insertion tube®, Medtronic Inc.,

Minneapolis, MN, U.S.A) were inserted into the cortex. The STN was physiologically localized by 4 tracks of microelectrode (microTargeting Electrode®, Medtronic) [1] simultaneously inserted. Microelectrode recording was started 15mm above the theoretical target and conducted by a manual microdrive device. Extracellular potentials were sampled at a rate of 24kHz by a surgical monitoring system (Leadpoint®, Medtronic) and the data were collected every 10sec at each depth. The discharge pattern of the neurons of subthalamus and substantia nigra pars reticulata (SNr) could be identified as follows: Characteristic neuronal discharges of STN were identified by the robust increase in background activity with multiple units with a relatively large amplitude and non-tonic irregular discharge pattern with a firing rate of around 30-60 Hz. As the electrode went beyond the STN, the background activity substantially decreased and the SNr cells with high frequency and tonic discharges appeared. The boundary between STN and SNr was not always clear; therefore, the ventral border of STN was defined by off-line analysis. The sensorimotor area of STN was distinguished by the modification of neuronal discharges in response to active and passive joint movement of contralateral limbs. The track recording the sensorimotor response of STN and a width of STN larger than 4mm was regarded as the eligible trajectory for DBS electrode implantation [14,16,17].

Local Field Potential recording by DBS Electrode

After the dorsal and ventral borders of STN were identified by MER, the DBS electrode (model 3389, Medtronic) with four platinum-iridium cylindrical surfaces (1.27mm diameter with 1.5mm length) and 0.5mm intervals was introduced to the microdrive device. The DBS electrode was mounted to keep a spatial relationship so that the center between the two lowermost bipolar contacts coincided with the depth of the microelectrode tip. LFPs were recorded by use of LeadPoint® system, too. The sensitivity was adjusted to 0.1mV/D in the display and the sampling rate was 24kHz. Using the lowermost two contacts (contact 0 and contact 1), the LFP was recorded from 15mm above the theoretical target down to 5mm beyond the theoretical target in a 1-mm step with filtration of 1-50 Hz. The patients were kept at rest without any voluntary movement during LFP recording, because the degree of synchronization of STN neurons in β-band is dependent on patients' movement [7,9]. The DBS electrode was not

advanced further than 5mm from theoretical target.

Macrostimulation and Implantation

The DBS electrode was withdrawn to the depth where the lowermost two contacts were located within STN as determined by MER, and the electrode location was confirmed by intraoperative roentogenogram. The parameters used for macrostimulation by DBS electrode were as follows: bipolar simulation with contact 1 (dorsal half of STN) as cathode and contact 3 as anode, pulse width 60 μsec, frequency 130 Hz. The muscle rigidity was significantly decreased by insertion of the DBS electrode even in the absence of electrical stimulation (microlesioning effect). In all cases, the amplitude could be gradually increased up to 5.0 volts without the generation of adverse effects, such as dysarthria, conjugate deviation or dystonic muscle contraction. After getting the optimal therapeutic effect by the refinement of the electrode position, the electrode was fixed with the Medtronic burr-hole cap. The final position of the electrode tip was consistently ascertained by intraoperative roentogenogram. The same procedure was then repeated for the other side. Finally, the patients underwent the implantation of an extension cable and an internal pulse generator under general anesthesia on the same day.

Frequency Analysis

Since the high background neuronal activity reflects both high frequency spikes and high neuronal density, the changes in the histogram of MER potentials are considered to correlate with both the neuronal density of STN and the spiking activity of neurons. Therefore, the standard deviation (SD) of 240,000 data points (24kHz for 10sec) of MER potential was regarded as a background activity at each depth and used as an electrophysiological marker of STN (Fig.1A, 1B). The background activity began to increase in a few millimeters above the estimated dorsal border before it turned into a steep increase in each trajectory. In order to avoid the vagueness of STN border in this study, the SD of MER potentials at each depth was expressed as a percentage of maximum SD in each patient and the depths where SD increased up to 50% of maximum and subsequently decreased down to 50% of maximum were defined as dorsal and ventral borders of STN, respectively (Fig.1C).

The power spectral density (PSD) was calculated by Fourier transform with

Welch's modification [20] over the 10sec sequence of LFP which is segmented into 1sec sections overlaid with a Hamming window, each with a 50% overlap. In the spectral density analysis of LFP around the dorsal border of STN, 9 data sets of MER and LFP records were aligned while assuming the depth of the dorsal border as 0 mm. In case of LFP analysis around the ventral border of STN, 9 data sets of MER and LFP records were re-aligned while assuming the depth of the ventral border as 0 mm. The maximum power was obtained in each band of θ (4-7Hz), α (8-13Hz), and β (14-35Hz). In particular, β-band was further divided into low β (14-20Hz) and high β (21-35Hz). The relationships between the DBS electrode depth to the dorsal and ventral borders of STN determined by MER and the LFP power of each band recorded by DBS electrode were analysed.

Statistical Analysis and Ethical Aspects

The LFP response recorded by DBS electrode is related to the level of activity of large groups of neurons. The PSD change of LFP with the depth does not always show the same trend as the background activity recorded by MER electrode. In order to test the significance of PSD increase and decrease of LFP with the location of the electrode, the correlation analysis between the normalized PSD and the depth of electrode located at from -2 mm to 2 mm around the ventral border or dorsal border of STN, respectively, was performed. In this analysis, both the correlation coefficient R and the P-value for testing the hypothesis of no correlation were calculated in each band of θ, α, and β. If P-value is less than 0.05, then the correlation coefficient R is significant. This study was approved by Research Ethics Committee, Kyushu University (No.20-16).

RESULTS

The width of STN determined by MER was 5.2±0.6mm along the eligible track for DBS electrode implantation. Figure 2 shows the representative records of 65 year-old male patient indicating the dependency of PSD on the depth of the DBS electrode from dorsal to ventral of STN through the trajectory, including the sensorimotor area detected by multi-track MER. The power of the low-frequency band clearly increased around the dorsal border of STN at -4 mm to the tentative target (0 mm depth) in Fig.2 and low-frequency synchrony were kept the same level beyond the ventral border of the STN; only the high β-power of LFP did show a clear decrease around the ventral border.

The summary of ten LFP recordings are shown in Fig.3, in which the depth-power relationships were aligned in reference to the dorsal (Fig.3B-E) and ventral (Fig.3G-J) borders, which are designated as 0 mm depth, respectively. Although the background activity in all MER data showed a steep increase around the dorsal border of STN (Fig.3A), the LFP power of each low-frequency band began to increase from a few millimeters above the dorsal border. As a whole, the depth at which θ-, α- and low β-powers reached almost half of the maximum power coincided with the dorsal border (depth 0mm); at the depth 2mm dorsal to STN, however, only high β-power reached half of maximum power (R=0.48, P<0.001, Fig.3E). As the DBS electrode advanced ventrally, the LFP power appeared to increase within STN or remained the same, and when aligned by the ventral border of STN, the LFP power of θ to low β band did not show any siginificant change around the ventral border (depth 0mm). Only the high β-power showed a small but significant decline just at the ventral border (R= -0.37, P=0.01, Fig.3J).

DISCUSSION

In this study, we performed an LFP recording from a DBS electrode to detect any change in spectral density of LFP specific to the borders of STN along the trajectory of the DBS electrode. An approximate 50% increase from the baseline in LFP power of low-frequency (θ- to low β-) bands correlated with the dorsal STN border; however, the LFP power of these bands did not show any significant change around the ventral border. Therefore, the increase in oscillatory activity in a low-frequency band is clear when the DBS electrode moves from Forel's field or zona incerta into the dorsal STN, while the decrease in oscillatory activity is unclear around the ventral STN. These results suggest that low-frequency LFP power recording by DBS electrode can be used only for the detection of the dorsal border of STN and the high β-power of LFP can help to detect the ventral border of STN.

Dopaminergic depletion in striatum induces the β-band oscillatory synchrony of neuronal activity in STN and globus pallidus internus, which contributes to the antikinetic effect on the basal ganglia in the "off" state of Parkinson's disease [11]. The use of β-power of LFP is reasonable for the electrophysiological localization of STN

[3,18]. An LFP recording by a DBS electrode has several technical problems to be overcome. A simultaneous recording of LFP and neuronal discharge revealed that the mean β-power (13-35Hz) was greater in dorsolateral STN than in ventromedial STN [10], and a majority of β-oscillatory cells were distributed in the doral STN [19]. Since these LFP analyses were performed by tetrode or multiple microelectrodes, the LFP signals were interpreted to originate from an area narrow enough to localize the borders of STN. However, the DBS electrode in the present study may have received the oscillatory LFP extensively from the surrounding structures other than STN, especially SNr. Therefore, the β-power recorded by DBS electrode did not show any clear distribution dominant in dorsal area of STN as explained in previous physiological studies [10,19] and anatomical study [12]. Moreover, the increase in LFP power was not specific to β-band frequency in the present study, which did not agree with microelectrode study by Trottenberg et al [18].

Furthermore, the thickness of the DBS electrode (1.27-mm diameter with a blunt tip) will cause a microlesion or microedema during insertion which is usually recognized as a transitory improvement of parkinsonian motor symptom (microlesioning effect) [4]. So, it is probable that the low-frequency oscillatory activity might have been considerably interfered by the intraoperative microlesioning effect of the DBS lead itself, as compared with microelectrode recording [10,18,19] or the DBS electrode recording after several days postoperatively [7].

STN-DBS is now accepted as a powerful surgical approach for advanced PD with intractable motor fluctuation [8]. An image-guided anatomical targeting and physiological verification of the nucleus with MER is crucial to achieve an accurate implantation of a DBS electrode in the sensorimotor part (dorsolateral region) of STN, which is commonly assumed to be the most directly related to the development of cardinal motor fluctuation in PD and therefore the best surgical target for DBS [6,21]. In particular, the physiologically determined width of STN larger than 4mm is considered to be one of the reliable determinants of an effective trajectory for STN-DBS [14,16,17]. The preliminary results from this study suggest that the dorsal border of STN can be estimated by the increase in low frequency powers recorded with the DBS electrode and a decline of high β-power may indicates the ventral border; however, further

physiological techniques for detecting the range of sensorimotor area of STN would be needed, such as synchronization or desynchronization of neuronal activity in response to motor task or stimulation [9], to replace the role of MER by DBS electrode recording.

CONCLUSION

In addition to MER study, a spectral power analysis of LFP recorded by DBS electrode is useful for the final confirmation of the physiological borders of STN in DBS implantation surgery. Further physiological studies and online data analyses are required to define the exact borders of sensorimotor STN, if subthalamic LFPs substitute the role of MER.

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FIGURE LEGEND

Figure 1

Method of off-line analysis of microelectrode recording (MER) in determining the electrophysiological border of STN. (A) The standard deviation (SD) of 240,000 data points (24kHz for 10sec) of MER potential was regarded as a background activity of each depth. (B) The relationship between the histogram of MER potential and the depth of each microelectrode. (C) The SD of MER potentials at each depth was expressed as a percentage of maximum SD in each patient and the depths where %SD increased up to 50% and subsequently decreased down to 50% were defined as dorsal and ventral borders of STN, respectively.

Figure 2

An example of power spectral density of local field potential around STN recorded by DBS electrode. (A) Raw data of MER and LFP obtained from a 65 year-old patient. LFP was obtained during advancing DBS lead after MER. (B) The relationship between the depth and power spectral density. The image was constructed by offline analysis using MATLAB (The MathWorks, Inc, MA). X-axis indicates the frequency in Hz and y-axis indicates the depth of the bipolar center of the lowermost contacts of the DBS electrode, advancing from 15 mm dorsal to 5 mm ventral to the tentative target (depth 0 mm) through STN. A color bar on the right represents power in $\mu V^2/Hz$.

Figure 3

Summary of off-line analysis of the background MER activity and low-frequency LFP power around STN. (A) The background activities in MER from 9 STNs were re-aligned in reference to the dorsal border (0mm) of STN, which was defined as a point of 50% increase of maximum SD from the base line. (F) Similarly, the background activities in MER from 9 STNs were re-aligned in reference to the ventral border (0mm) of STN, which was defined as a point of 50% decrease from maximum value. (B-E, G-J) The relationships between the depth along the trajectory and LFP power of low-frequency band. The data were expressed as mean (thick line) ±SD (grey zone). Changes in LFP powers were re-aligned in reference to the dorsal border (B-E)

and the ventral border (G-J). (B, G) θ band, 4-7Hz; (C, H) α band, 8-13Hz, (D, I) low β band, 14-20Hz; (E, J) high β band, 21-35Hz. The negative and positive values in depth mean dorsal and ventral to the border (0 mm), respectively.

Figure 1

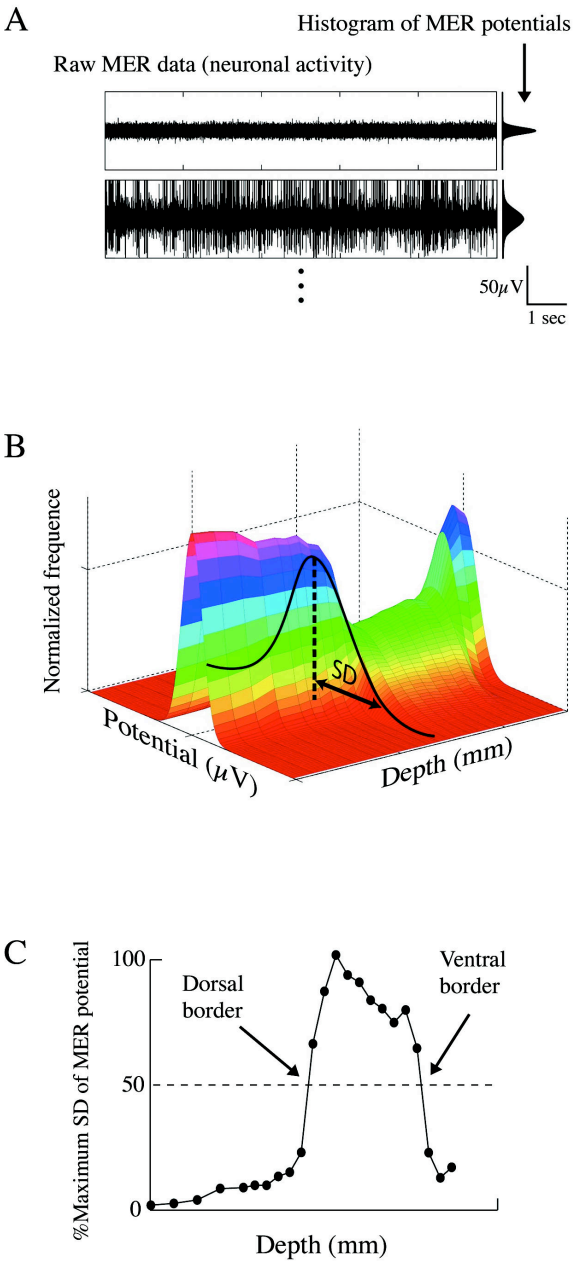
A
Histogram of MER potentials
Raw MER data (neuronal activity)
50μV
1 sec
B
Normalized frequence
SD
Potential (μV)
Depth (mm)
C
%Maximum SD of MER potential
100
50
0
Dorsal border
Ventral border
Depth (mm)

Figure 2

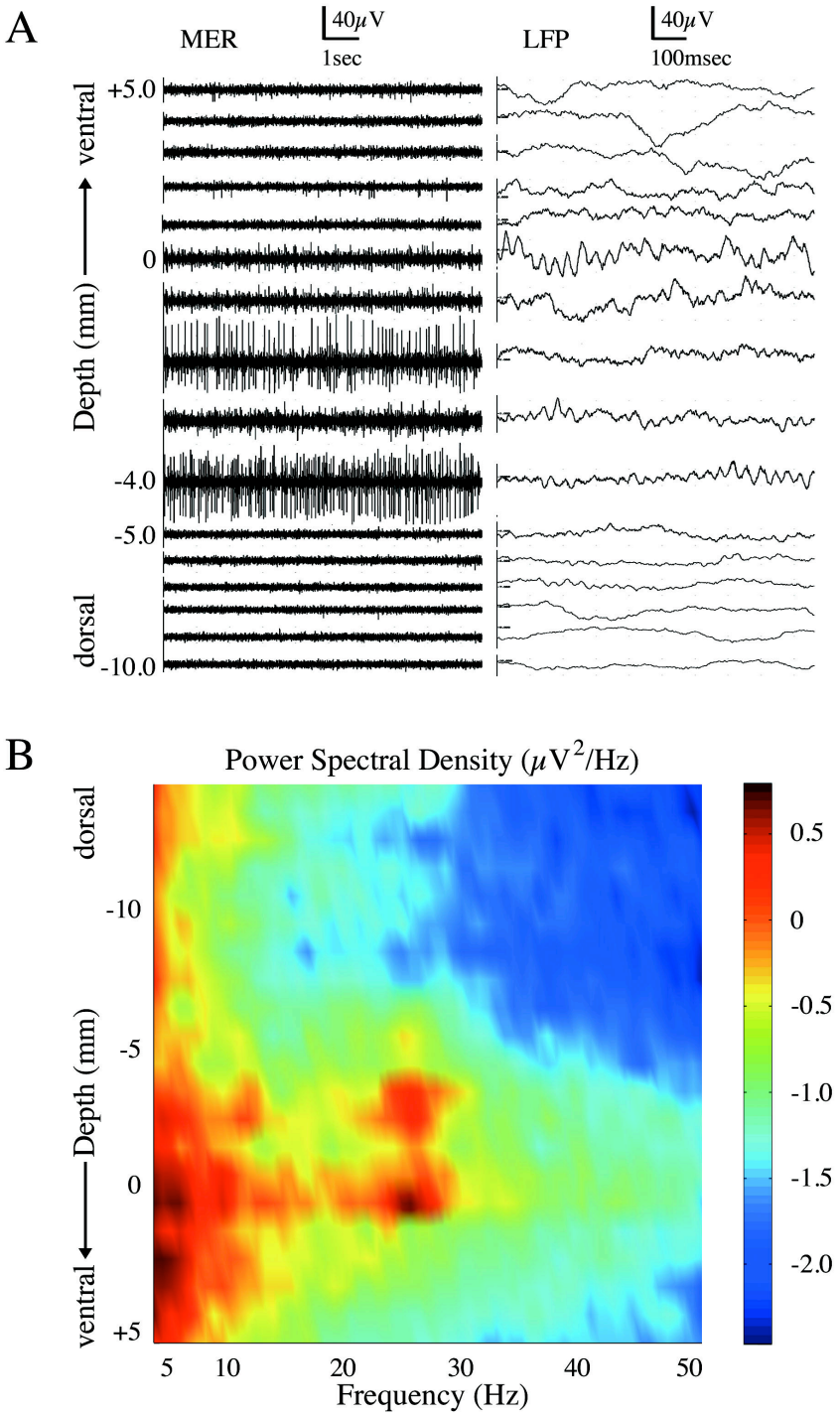
A
MER
40μV
1sec
LFP
40μV
100msec
+5.0
ventral
0
Depth (mm)
-4.0
-5.0
dorsal
-10.0
B
Power Spectral Density (μV²/Hz)
dorsal
-10
-5
0
ventral
+5
Depth (mm)
5
10
20
30
40
50
Frequency (Hz)
0.5
0
-0.5
-1.0
-1.5
-2.0

Figure 3