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The reliability and validity of functional brain connectivity compared to a self-reported measure of pain

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Pain is a multidimensional perception that is complex in nature. It is a unitary construct that includes overlapping domains such as intensity, affect, quality, and frequency. These domains do not reflect the amount of tissue damage. It reflects the end result of the perception of pain in which multiple biopsychosocial factors are involved (Gatchel et al., 2007). Multiple self-reported measures have been used in an attempt to capture most factors that may influence pain such as psychological factors. However, there is no one scale that can be used to characterize pain as a whole with all its factors. Furthermore, physical measurements did not prove to be better than self-reported measure in pain characterization. Since pain perception is believed to occur in the brain, it seems rational to measure aspects of the brain as a biomarker for pain. One method that has been recently used is functional connectivity magnetic resonance imaging (fcMRI), which is a measure of the connectivity between brain regions that are previously known to be related to pain.

In this paper the focus will be on the recent “physical measure” of pain in comparison to the self-reported measure, the Gracely box scale. First a summary of the reliability and validity of the Gracely box scale will be mentioned. Then the development of the functional connectivity based on the fMRI studies will be

addressed. Finally, I will assess the reliability and validity of the measure compared to the Gracely box scale.

The Gracely box scale

The Gracely box scale has been established based on extensive cross-modality matching studies (Gracely et al., 1978a; 1978b; and 1979). The main goal back then was to incorporate another dimension of pain, i.e. the affective dimension, and to provide a scale that is ranked on a ratio scale of measurement. Also, they used pain descriptors anchored to a numeric value so subjects can determine their exact level of pain intensity or unpleasantness. Therefore, reducing the variability compared to unidimensional numeric pain scales (e.g. visual analog scale) and increasing the sensitivity of the scale.

Descriptors of pain intensity and unpleasantness were taken from a previous study that collected words that are used to describe pain in the clinic and were categorized to different dimensions of pain (Melzack and Torgerson, 1971). Gracely et al. (1978a) took fifteen words from those lists to describe pain intensity and 15 words that are used to describe unpleasantness and performed experiments where subjects match each word descriptor to a physical modality (e.g. handgrip force or time duration), a technique called “cross-modality matching”. Then power function exponents were calculated and correlation coefficients were determined between the groups, within groups and between sessions. Based on the similar power function exponents the validity of the descriptors with their ranked orders was established. Furthermore, results of the correlations support the face and content

validity of the scale as well as test-retest, intra-rater, and parallel-groups reliability. In addition, the internal consistency of the scale was confirmed by the high individual-item repeat and the item-group correlations. Adjustments were made to the descriptors to include a total of 13 descriptors for intensity and 13 for unpleasantness (Gracely et al., 1978b).

The discriminant validity of the scale was established based on two studies that tested the scale when administering a drug (diazepam) that is known to reduce the affective aspect of pain but not the intensity (Gracely et al., 1978b) and, conversely, when administering a different drug (Fentanyl) that is known to decrease the intensity of pain but not the unpleasantness (Gracely et al., 1979). The scale was sensitive enough to discriminate between the 2 dimensions of pain. Further, the scale was translated to French and compared to the visual analog scale providing evidence for concurrent validity (Duncan et al., 1989). Also, Heft et al. (1980) examined the transferability of the scale to clinical pain establishing its external validity. Finally, the scale has been used in various clinical population studies such as orofacial pain (Blakey et al., 1996) and fibromyalgia (Geisser et al., 2007).

Although most forms of reliability and validity has been satisfied for the Gracely box scale, predictive validity and criterion validity are still absent. While the scale has shown great ability to discriminate between the two dimensions of pain, it has not shown the ability to discriminate between acute and chronic pain patients or predict transition to chronic pain. A measure or scale that has such ability would

be of great use in clinical pain populations as patients with chronic pain has been shown to be less responsive to treatment (Borsook and Becerra, 2000). In addition, due to the absent of a gold standard in pain measurement, criterion validity has not been determined. Another limitation of the Gracely box scale is that it only captures two out of many domains of pain. Other dimensions such as quality and duration are important, especially in musculoskeletal pain. Lastly, as with all self-reported measures, it is affected by other psychosocial parameters such as decision-making, mood, situational elements, and expectations. For example, subjects' decisions in reporting more or less pain are affected by the situations in which it is administered, their expectations and mood (see McGrath [1994] for review).

The functional connectivity magnetic resonance imaging (fcMRI)

Since the brain is considered the “hub” of pain perception, it seems reasonable to measure specific brain activity as a biomarker for pain. One approach that has been used over the past decades is to measure brain activity through functional MRI. This method measures the neural activity indirectly by evaluating the changes in blood flow in the capillary beds (logothetis, 2002). However, one limitation is that evaluating the Blood oxygen level dependant (BOLD) signal cannot distinguish between excitatory and inhibitory neurons, as both would increase the blood flow to the brain area. In addition, blood volume and blood flow give opposite affects in the net BOLD signal therefore affecting the resulting relationship between the neuronal activity and BOLD response (Borsook et al., 2011). Despite these limitations fMRI has definitely increased our understanding of pain processing in

the brain. With it, key regions have been identified that are important in patients with chronic pain and acute pain. Finally, fMRI provided the foundation for other techniques to be applied, as will be discussed later.

A recent method based on functional MRI (fMRI) that has been shown to have a promising future in characterizing pain in the brain is functional connectivity (fcMRI). This method evaluates the functional oscillations among brain regions or their relative synchrony (Shackman et al., 2011). It provides a comprehensive analysis of the network activation of brain regions that are pain-related. In using this method a correlation map is constructed between the brains' regions of interest (ROI) and correlation coefficients are calculated between the BOLD signal time course and the time variability of other brain voxels (Baliki et al., 2008).

A recent study that had used this method sparked my interest and the interest of other researchers in using this method. Baliki et al. (2012) examined the functional connectivity of the brain in patients with acute low back pain followed over one year. The patients were subsequently grouped to a back pain persistent (SBPp) group (i.e. the patients who develop chronic pain) and a back pain recovery (SBPr) group (i.e. those who recovered). The results of the fMRI of the first visit show that the connectivity between the medial prefrontal cortex and the nucleus accumbens (mPFC-NAc) predicted patients who transitioned to the chronic group using the area under receiver-operator characteristic (ROC) curve and discrimination probabilities (D value= .83). That means that the mPFC-NAc connectivity at baseline had 83% prediction probability of the group that

transitioned to chronic pain. Specifically, patients who did not recover (SBPp) had higher mPFC-NAc connectivity at baseline than the group that recovered (SBPr). Interestingly, the only difference between the two groups at baseline was in the results of the affective component of the McGill Pain questionnaire (MPQ). The MPQ is a self reported scale similar to the Gracely box except that it has more than 2 dimensions of pain (quality, affect, and intensity). These results provides great prediction validity of the tool. However, this was the first study of its kind; meaning that it was the first study to evaluate fcMRI in a clinical population and use it to predict the transition to chronic pain. Therefore, not many studies were found to evaluate the reliability of this technique in studying pain.

Three studies were found that examined test-retest reliability of the pain-related BOLD signal in fMRI. Quiton et al. (2014) measured the intersession reliability of pain related networks in the brain in healthy individuals' responses to a painful heat stimulus. The intra-class correlations (ICCs), which is a measure of test-retest reliability, ranged across days from .31 to .78. Letzen et al. (2014) evaluated the test-retest reliability of pain-related BOLD signals in fMRI in healthy individuals in response to a thermal stimulus across 3 runs of fMRI scans performed in the same visit (within subject reliability). ICC results in this study ranged from .32 to .88, indicating poor to good reliability. Finally, Updadyay et al. (2015) evaluated intersession reliability with similar ICC results ranging between .5 and .85 for different brain structures.

Only one study was identified that examined the test-retest reliability of the fcMRI technique, similar to the method used by Baliki et al. (2011), and compared it to the reliability of the visual analog scale (VAS). In this study, 32 healthy subjects performed 3 consecutive fMRI scans in the same session (intersession reliability) with responses to painful thermal stimuli. Brain connectivity analyses were performed between pain-related regions and VAS ratings were collected in response to the thermal stimuli. ICC results for the fcMRI ranged from .174 to .766 for the different pain-related connectivity networks. However, the highest reliability (ICC; .649 to .766) was for the mPFC-NAc network, the same network that predicted the transition to chronic back pain in Baliki et al. (2012). In contrast, ICCs for the self-reported measure (VAS) ranged between .906 and .947, indicating excellent test-retest reliability (ref). Furthermore, the Gracely Box scale, presented previously, has reported test-retest reliability of .89 to .96 (ref). These results suggest that the reliability of the fcMRI method may be of lower magnitude than the reliability of self-reported measures of pain.

Since reliability is a prerequisite of validity, the validity of the use of fcMRI in quantifying pain is questionable. Several factors may contribute to this wide range of results. Duration of scan, type of analyses, networks analyzed, modeling and preprocessing, and head motion analyses are all factors that can contribute to the increased variability in reliability results. Additionally, the increased number of variables that are analyzed in the fcMRI results may also contribute to the increased variability in the reliability results compared to the self-reported measures. It is important to point out that the mPFC-NAc connectivity produced high enough ICC;

meaning that the reliability for using this measurement analysis as a group (i.e. in research studies) is good. However, the translation of this method to the individual level, meaning using it in clinical situations to predict who transitions to chronic low back pain, for example, may not yet be appropriate. Future studies should report the test-retest reliability for the analyses they perform and investigate the concurrent validity of this measure.

In conclusion, the analysis of functional connectivity of the brain seems to have high predictability in regards to the transition to chronic pain. However, the test-retest reliability, as measured by the intraclass correlation coefficients, of the measure as a mean to characterize pain is low compared to the Gracely Box scale. The Gracely box scale, on the other hand, was not tested to examine its predictive capabilities. Given the complex nature of pain, both measures may be used to study pain in order to have a highly reliable scale (the gracely box) and a highly predictive scale (fcMRI). In future studies, it would be nice to see whether the fcMRI technique correlates with the Gracely Box scale. Finally, a standardized protocol is needed for the use in other labs to reduce between-labs variability.

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