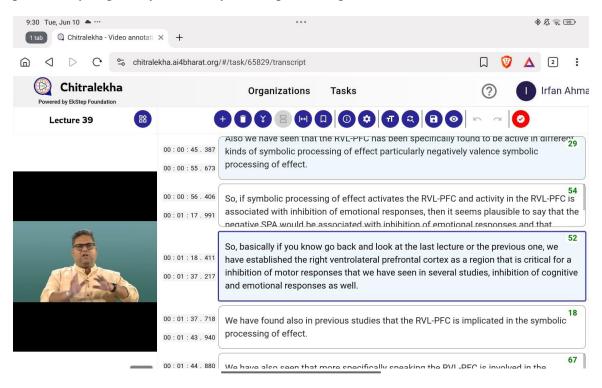
Social Behavior and the Brain: An Introduction to Social Neuroscience Dr Ark Verma Department of Cognitive Sciences Indian Institute of Technology Kanpur Week - 08 Lecture - 39

Hello and welcome to the course social behavior and the brain and introduction to social neuroscience. I am Dr. Ark Verma an associate professor in the department of cognitive science at IIT Kanpur. This is week 8 of the course and we are in the 39th lecture where we are trying to understand about the symbolic processing of effect and the role that the RVL PFC actually plays in that. Now so far we have seen that the right ventrolateral prefrontal cortex activity is associated with the inhibition of motor, cognitive and affective or emotional responses. Also we have seen that the RVL-PFC has been specifically found to be active in different kinds of symbolic processing of effect particularly negatively valence symbolic processing of effect.



So, if symbolic processing of effect activates the RVL-PFC and activity in the RVL-PFC is associated with inhibition of emotional responses, then it seems plausible to say that the negative SPA would be associated with inhibition of emotional responses and that activity in the RVL-PFC would be largely you know responsible for this effect. So,

basically if you know go back and look at the last lecture or the previous one, we have established the right ventrolateral prefrontal cortex as a region that is critical for a inhibition of motor responses that we have seen in several studies, inhibition of cognitive and emotional responses as well. We have found also in previous studies that the RVL-PFC is implicated in the symbolic processing of effect. We have also seen that more specifically speaking the RVL-PFC is involved in the processing of negatively valenced effect, symbolic processing of negatively valenced information in regulation of that in you know and it does so by modulating the activity in the of the areas that are typically involved in the limbic circuit or the processing or the areas that are responsible for processing of emotional information.

So, that is what has been established so far. The chronology seems to be that if you are experiencing negative emotions and you want to inhibit them basically that is where the RVL-PFC will come into play and it will inhibit the you know feeling of negative you know effect by down regulating the activity or the you know activity of the limbic areas. Now prior to the studies that have directly linked the symbolic processing activity, symbolic processing of effect with the down regulation, several studies have also addressed the same without you know directly asking this question out aloud. For example, Hornak and colleagues tested a sample of patients with VLPFC damage and found that these patients were impaired at explicitly recognizing emotional facial expressions and emotional voice tones. So, these people had a damage in the ventral prefrontal cortex.

So, VLPFC And that they were impaired at explicitly recognizing. They might be able to implicitly understand and react that oh this is a happy face, sad face and so on. But if you ask them to name this that oh whether it is a happy face or a sad face, people are not being able to do that. So, this is this sample of patients. Now, within this group 9 out of 11 patients had either right or bilateral ventral cortex damage and 8 of these were impaired in one or both of the symbolic crossing of effect tests.

Of the two left only ventral prefrontal patients, one performed well above the mean of the non-ventral controls. So, basically you know people who are relevant for our study is basically the nine people who are either right damaged or damaged on the both sides of the ventral cortex. Additionally, the extent of impairment that these patients show in the symbolic processing of effect tasks was found to be regulated with this inhibition of emotional behavior suggesting that this impaired ability to engage in the symbolic processing of effect is associated with more emotional behavior and that this association may be related to the ventral prefrontal impairment. So, what is basically happening is that if the right ventral or bilateral ventral prefrontal cortexes are damaged, then it leads to more emotional behavior, then it leads to more impulsivity and that is where basically you will see that these patients differ with the patients who had left only ventral damage or who had no ventral damage. Hariri and colleagues for example, just taking a different

study, demonstrated the first evidence of a complete pathway from the symbolic crossing of effect regions to RVL-PFC activity to reduced amygdala activity.

Remember in the previous lecture we were talking about the RVL-PFC modulating the activity in the amygdala, also modulating the activity in the anterior insula. and governing the phenomenal experience of negative emotions such as social pain and rejection or even you know physical pain. Now in Hariri and colleagues study participants judge the emotional identity of a target's facial expression. However, the trials varied with respect to whether symbolic processing was actually required or not required to make this judgment. So, here you know facial emotion recognition task is there, but the variations was that in one case they had to symbolically process it, put things into words and in the other variation they did not have to do that.

So, in the SPA condition, where effect labeling was explicitly required, a target face was presented at the top of the screen with two emotional words, angry and surprised. So, you basically have to look at that face, look at that facial expression and link it to one of the words, either it is angry or it is sad. So, here explicit symbolic processing of effect is being invoked. And participants had to choose so as I said participants had to choose which of the words best describe the target faces emotion. In the non-SPA condition they had to do what is called the effect match.

So there is one face here and there are two faces here and they basically just have to match which of the two you know which of the bottom two faces are having the same expression at the face on the top. So, here you will see this can be done pre-verbally as well you just have a judgment of okay this is feeling happy this feeling happy you match it you do not have to put that thing into word okay. So, there is no symbolic processing of effect required in this condition alright. So, two conditions SPA condition non-SPA condition the task is facial emotional judgment. Now according to Hariri and colleagues in the non-SPA condition participants basically could match the faces based on just perceptual characteristics such as wide eyes, furrowed brows, clenched teeth but they did not really need to you know judge or interpret the information you know verbalize that information that was not required.

And indeed, if you look at these stimuli, if you look at a bunch of these face stimuli, there is a strong sense of pop out in the non-SPA stimuli in which the faces that match seem to automatically come together. See, there are a lot of Gestalt principles that operate when you are evaluating visual information. and similarity is one of them. So, if you find similar expression on two faces they will automatically seem to be grouped together while the third will be kept out and in that sense you can take that judgment on whether these effects match or do not match at a very pre-verbal sort of level itself at a very lower level you do not need to cognize and understand what expression and see whether it is

anger whether it is sadness you do not have to go through all of that. Also, in this non-SPA condition, there was significant amygdala activity.

Remember, we have been talking about how amygdala is involved in immediate and a quick calculation of facial emotion expression, negative expressions, you know, more specifically fear, threat and those kind of things. So, in the non-SPA conditions, they observed that there was significant amygdala activity relative to when shape matching was done. So, matching triangle with square, square with, you know, triangle with triangle, square with square. In, in that case, ah, amygdala activity was not there. So, effect matching amygdala activity is very critically found.

Instead, SPA, ah, and in, in the other condition. So, we have talked about the non-SPA condition. What is happening in the SPA condition? In the SPA condition, the activity, you know, SPA condition was associated with activity in the right ventrolateral prefrontal cortex and the fusiform face area. the latter presumably indicating that the target phase was still being attended to in the SPA condition. So, we are not only you know analyzing the facial emotional expression and putting it into words, but we are also doing that extra job of you know analyzing the perceptual characteristics.

So, that is where probably the fusiform phase area is coming active, but the right ventrolateral prefrontal cortex seems to be involved in the symbolic processing of effect when it is recruited in the SPA condition. So, again something that echoes consistently with the previous research that we have seen. Now, when the direct comparison was performed between the SPA and the non-SPA trials, greater RVL-PFC and diminished amygdala activity was observed during SPA trials, okay. Thus, two different forms of emotional processing seem to be at work here. One is symbolic processing and the other is non-symbolic which seems to be routed through different set of neural systems basically the amygdala and the limbic circuit, alright.

And given that the amygdala has been shown to be involved in multiple studies of effective processing to be activated by conditions that would allow only automatic processing, we have seen how amygdala was activated in you know automatic activation of stereotypes, automatic activation of threat information and so on. even when subliminal presentations etcetera were being done, it is quite surprising to see that the amygdala was not responding you know the amygdala activity is rather subdued under conditions that would allow for both automatic and controlled processing. So, this is again a very interesting insight that comes through you know the studies specifically this Harari and colleagues study. Now, in another follow up study, the authors compared the SPA and non-SPA processing in the context of race, ok. So, you have seen the several experiments talking about race in the previous lectures.

So, just let us look at this as well. Rather than using different facial expressions of emotions, these time the authors actually used all neutral faces, just the expressions varied by race. So, for example, neutral expressions in a white Caucasian face versus a black American face, just neutral expressions are there. Now, in USA typically even if there is a neutral expression, the stereotype that is there for the blacks are generally evaluatively negative. So, if you showing a black face to a white American it seems to trigger some sort of negative stereotypes which is coming through baggage this that you know cultural stereotypes what not alright.

So, the stereotypes of blacks are evaluatively negative particularly when it is being judged implicitly. So, we have seen a lot of times that when participants are explicitly asked about this, they profess to be egalitarian, they don't want to you know respond in a biased or in a discriminatory manner, they don't want the stereotypes to be influencing them but at the you know at the implicit level these stereotypes get activated and they need a lot of regulation for them to not overtly you know influence behavior. So, and this is very interesting that these negative stereotypes for blacks are not only found in white American participants but they are also found in black American participants who seem to also be having more negative implicit stereotypes of blacks than of whites. So, this is a very interesting sort of you know finding that is reported in research. Now consistent with these behavioral findings a number of neuroimaging studies have observed greater amygdala activity to black rather than to white faces you can see you know a lot of previous lectures we have talked about this already at least to the extent that the participants accept possessing you know strong anti-black implicit stereotypes.

So obviously where the stereotype is there and the participant accepts to it and it is present. It does lead to very high amygdala activity which could either be coming through negative evaluation or it could be coming through perception of threat of some kind basically through you know the activation of cultural stereotypes. Now these authors they reason that because even a neutral expression of black face produces a similar amygdala response as a negatively expressive white face engaging in SPA by labeling the race of a black target might disrupt this race related amygdala activity, okay in much the same way that affect labeling disrupts the amygdala response to negatively expressive faces. So, this is what they want to sort of see.

So, they want to basically capture the symbolic processing of this race related stereotype and in the hope that when you sort of ask people to name the race and so on it will bring that stereotype, verbalize that stereotype, afford symbolic processing to that stereotype in much the same way that was responsible for the disruption of negative effect. So, we are basically expecting a disruption of this negative racial stereotype. Let us see what happens. It is what and again there is another hypothesis that is there. So, it is worth noting that the another reasonable hypothesis would be that the race labels would focus attention on the onto the negative stereotype aspect of the targets that is race than on the

other more neutral or positive aspects and would therefore, lead to producing greater activity in the maker.

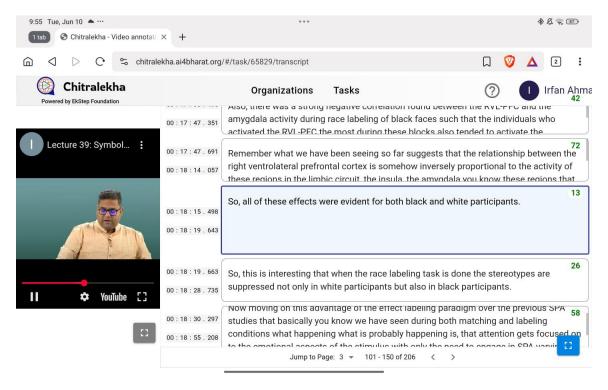
So, if you ask people to explicitly talk about race two things can happen either due to the RVL PFC activity and down regulation etc. ah the overall thing will be dampened and subdued or it will actually even get more magnified ok. So, both alternate you know both slightly competing hypothesis were present. Now, what happens as in as in other fMRI studies that we have seen so far the authors actually observed greater amygdala activity to black faces than to white faces when the participants were performing just a race match task ok. Again we have seen effect match task or the race match task here does not require symbolic processing, it does not require you know actually putting into words what you are seeing.

Authors also observed the same separately for both white and black participants. So, this race racial stereotype interestingly is present in both white participants as well as black participants. So, interestingly black participants also produce greater amygdala activity to black faces than white faces consistent with the previous behavioral findings you know of displaying black you know negatively evaluated stereotypes to black faces. Again something that we have talked about in much detail in the past. Interestingly, in contrast to the non-SPA condition, when participants were actually performing the race label task, there was no differential amygdala activity to black and white faces.

So, here you can see that the kind of you know suppression of this racial stereotype we were hoping for is actually present. And the amygdala responses to black faces actually diminished compared to the amygdala responses that were being observed during the race match task for black faces and even compared to the control task where there were no faces involved at all. So it seems somehow verbalizing or symbolic processing is capable of even suppressing this racial stereotype which on the other hand was operating very well in the race label in the race match task at a very implicit level. Now what is driving these effects? Again as expected there was greater RVLPFC activity during the race label task or race label of black faces but not during the race labeling of white faces because again in that case it was not even necessary. Also, there was a strong negative correlation found between the RVL-PFC and the amygdala activity during race labeling of black faces such that the individuals who activated the RVL-PFC the most during these blocks also tended to activate the amygdala the least.

Remember what we have been seeing so far suggests that the relationship between the right ventrolateral prefrontal cortex is somehow inversely proportional to the activity of these regions in the limbic circuit, the insula, the amygdala you know these regions that are responsible for us for feeling this negative effect as and when the higher RVL-PFC activity kicks up it reduces the activity in the amygdala and the insula and the such. So, all of these effects were evident for both black and white participants. So, this is

interesting that when the race labeling task is done the stereotypes are suppressed not only in white participants but also in black participants. Now moving on this advantage of the effect labeling paradigm over the previous SPA studies that basically you know we have seen during both matching and labeling conditions what happening what is probably happening is, that attention gets focused on to the emotional aspects of the stimulus with only the need to engage in SPA varying across conditions. When SPA is required only then the SPA gets recruited otherwise you can basically go on with the emotional sort of you know with the implicit sort of processing of affective information.



Affect labeling therefore it seems that it requires symbolic processing whereas effect matching does not require symbolic processing although effect matching does not prevent spontaneous symbolic processing in in some sense you're still cognizing even if you're not speaking out aloud you're still cognizing at an internal level oh this is a black participant white participant this is a you know angry emotion you know sad emotion or happy emotion that spontaneous SPA is still happening but it is not happening at the explicit level. So at the explicit level effect labeling is what is basically being recruited. Also what might be happening here is that by using verbal labels that appear in different positions across trials participants are not being able to learn a stimulus response mapping for example between perceptual cues of fear and a right button press so that kind of learning is is not really happening because you are basically doing this verbal mapping when they are doing this labeling task they need to read the labels on each trial to which options are available and they respond accordingly they don't implicitly respond to happy right button sad left button and so on Now despite these advantages that are you

know embedded in the affect labeling task, there were some inferential limitations present in the original you know formulation of the effect labeling paradigm. So, there is only so much that you can get from this kind of task and this is basically something that you know we should now discuss. So, although the comparison of the affect label ah to affect match condition ah represents a comparison of the SPA and the non-SPA conditions basically this distinction is probably confounded with other differences between the two kinds of tasks as well the ah you know the labeling and the matching tasks.

For example, firstly effect match trials present three faces of which at least two are posing negative emotional expressions on most trials. In contrast, affect label trials basically present just a single face and then there are two words. So, the amount of stimulus information or the nature of stimulus information is different in the two tasks. So, one could actually argue that the greater amygdala activity that is presented in the affect match task is probably because there are more amygdala activating stimuli that are being presented on the slide as opposed to in the affect labeling condition where there is just one amygdala activating stimulus that is the face and there are two words. So, again this these kind of interpretations should be paid attention to while understanding or interpreting the effects of these studies.

However, this does not seem to be a complete argument, it does not seem to be entirely satisfactory given that a single negative expressive phase even if presented subliminally is typically found sufficient to produce you know amygdala activity whereas, neither of the two affect labeling studies reported the presence of amygdala activity during the labeling condition. While it is true that the affect matching condition had three face, affect labeling condition has one face, even if one face is there, one face itself is enough typically and a lot of studies have shown that is enough to activate the amygdala enough. Interestingly in these conditions when you are doing the comparison in the affect labeling condition none of these studies are reporting amygdala activity. So, it seems that something has really suppressed the amygdala activity in these conditions which is probably by virtue of recruiting the RVLPFC. Now, another theoretical possibility could be that effect labeling is not really affecting amygdala activity, but rather affect matching leads to hyper amygdala responses and thus the difference between two condition emerges.

So, it is kind of a reverse you know argument that is been presented here that it is not that affect labeling is suppressing amygdala responses, but that affect matching leads to hyper amygdala responses and therefore, the differences that we see are there. Now again this criticism also does not really address the issue of why there was no amygdala activity observed during the affect labeling condition. Even if we accept this you know condition or this explanation it does not you know tell us why there was no amygdala activity observed during the affect labeling condition. So, some kind of symbolic crossing is

certainly happening and that probably is behind this. But it does raise this very interesting or important issue that affect matching has different task requirements than affect labeling and affect matching typically provokes the amygdala activity you know more such as by passive you know observation of faces or making you know gender judgment for faces.

So, again what we should take away from this discussion is that the task requirements from affect labeling and affect matching are relatively different and hence the results that we are sort of taking out of this ah should be taken with a pinch of salt. We should be very conscious of the fact that there are these differences present between these two paradigms. So, it is not really known how much the difference between the labeling and the matching paradigm you know how much of this difference between the labeling and the matching conditions results from each of these two factors that we are just discussing because passive observation condition has not yet been included in any of the studies that we have discussed so far. So, this last criticism because we have not you know seen studies including the passive observation thing, it acknowledges at least the fact that the labeling condition is indeed modulating the amygdala activity, but it takes issue with where this modulation is coming from. So, again we need to know where is this happening from, what is the you know cause, how is this really taking place.

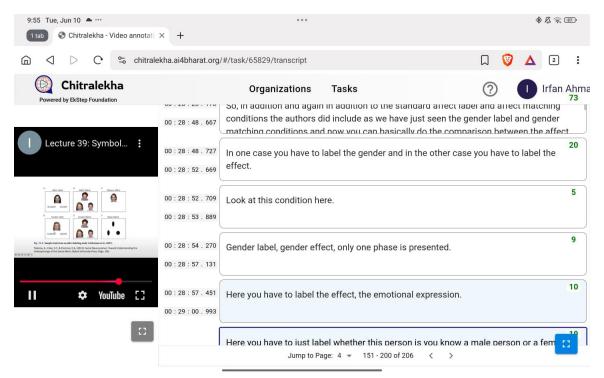
So, although the authors have characterized the affect labeling task in terms of SPA and non-SPA processing ah one could just as easily label them as cognitive and perceptual processes more generally without really making any claims about the affective component of these tasks. So, given that we have demonstrated we have just seen that the task requirements are very different ah we can call them SPA and non-SPA task, but we can also call them an affective or ah cognitive task you know in one case you have to do the just the perceptual matching of this effect of this phase versus this phase versus this phase you are just doing a perceptual matching and in the other case you actually have to cognize you have to look at the verbal label and you have to see whether this verbal label corresponds to this phase presented here ok. So, all what we have sort of inferred so far from the SPA and the non-SPA condition we should take it with a pinch of salt is what the message is. Now, in other words perhaps any kind of cognitive or verbal labeling process will diminish the amygdala response to the emotional stimuli. Again you can see that while we are sort of you know criticizing this particular paradigm at this point, the basic message remains the same.

The basic message still remains that any kind of cognitive or verbal labeling of emotional responses does diminish amygdala activity, does diminish the responses from the limbic system. So to address all of these concerns together, the authors ran a bit of a modified version of this labeling task that included a number of control conditions as well. So this is Lieberman's study in around 2007. Now, all of these conditions I will just show you that these are the conditions. So, you have the effect label task where you basically just

label the task whether this is an angry face or a scared face, you have the effect match task you have to just match this expression with the expression on any of the two bottom faces, you have just the passive observation task as well.

And then you have the shape match task, you have the gender match task and you have the gender label task. So, these three are affective tasks A, B and C and these three are where effect is orthogonal to the actual task alright. Now, the authors have included here as I just showed a passive observation condition during which subjects were presented with a single negative emotional target and now you can see how much amygdala activity that will actually prompt. This condition was specifically introduced to construct regions of interest in the amygdala which could then be compared across all of these other conditions. So, affect label, affect match, gender match, gender label, gender match and so on and to examine the modulatory effect of all other forms of stimulus processing that are being created.

So, in addition and again in addition to the standard affect label and affect matching conditions the authors did include as we have just seen the gender label and gender matching conditions and now you can basically do the comparison between the affect label and gender label which basically serves as the most critical comparison as both conditions present only a single target phase and both involve labeling albeit different kinds of labeling. In one case you have to label the gender and in the other case you have to label the effect. Look at this condition here. Gender label, gender effect, only one phase is presented. Here you have to label the effect, the emotional expression.



Here you have to just label whether this person is you know a male person or a female person. So, this is a very interesting critical you know comparison that we are going to see here. Now, as is seen in the results affect match, gender match and gender label all three conditions produced amygdala activity that was statistically equivalent to the activity produced during the passive observation of emotional phases. So, in the observed conditions, all of these you know conditions basically produce the same kind of amygdala activity that was produced in this passive observation condition as well.

Only affect labeling produced significantly less amygdala activity than the observed condition. So, it is even lower than the baseline which basically should tell us that some kind of suppression, some kind of modulation of amygdala activity is certainly being recruited or exercised over here. Now, affect labeling also produce less amygdala activity than even gender labeling or affect matching indicating that this affect is really coming from the symbolic processing of affect that we have been arguing so far for rather than the number of stimuli faces that are there on each trial or the different kinds of cognitive or perceptual processes that are at play here in these tasks. So, incidentally in the whole brain analysis a number of limbic and paralimbic structures were also found to be less activated during affect labeling than gender labeling including the dorsal ACC, the subgenual ACC, the posterior insula and the ventromedial PFC. Again the areas of the limbic and the paralimbic region which are typically involved in different kinds of affective information processing.

Now in contrast only a single region of the brain which is the RVLPFC was found to be most active during affect labeling than gender labeling. So, here again you can see that the you know RVLPFC is getting recruited in cases of affect labeling which is probably because this task or this condition requires symbolic processing of affect. In addition, after running a correlational analysis using the amygdala cluster that they had initially identified from the comparison of affect and gender labeling you know areas as seed, the authors found that the RVLPFC was one of only two regions that had a negative correlation pattern of activity during this comparison. So, it is something that the more affective information you are processing, the lower sort of activity in the RVLPFC is there, and the more and the more you are suppressing that activity the higher you know range of activity is seen in the RVL-PFC.

So, all in other words if one wanted to really know which subjects produce the least amygdala activity during affective labeling relative to gender labeling, you just needed to find out the who had the most activity in the RVL-PFC and that would basically give you the right results. So, again as I have been saying it seems that the activity of the right ventrolateral prefrontal cortex seems to be inversely proportional to the activity in the areas of this limbic region which are involved in emotional or affective information processing. So, interestingly here if you look at this with respect to the medial prefrontal cortex also this was also one region that was you know showed this similar pattern. So,

the two regions that are responsible most for regulating information is the RVL-PFC yes and also the medial prefrontal cortex. And this is interesting because the medial peripheral cortex has been you know initially identified as a possible mediator of the RVL-PFC effects on amygdala.

Remember we are talking about how RVL-PFC does not have dense projections to amygdala but the MPFC has very dense projections to amygdala but RVL-PFC has dense projections to the medial peripheral cortex. So it is through this indirect connection it seems that the amygdala activity is being modulated by this RVL-PFC. Additionally, the medial peripheral cortex has also been found in several studies critical to extinction processes and the regulation of the amygdala in the current context that we are just seeing and has traditionally been associated with reflective emotional process. So, this area on its own also is you know considered relatively important ok. Now, when they ran a mediational analysis basically seeing where this effect is coming from the RVLPFC leads to activity in the MPFC which leads to activity in the amygdala pathway seems that this relationship between the RVLPFC and amygdala during the affect labeling was significantly mediated by the MPFC activity.

So, the initial neural hypothesis that we were you know proposing in the previous lecture sort of seems to get you know supported by the results from this particular study. Now, they also performed a psychophysiological follow up and in in that the authors found very similar results for skin conductance paralleling the amygdala findings in fMRI research and let us look at this psychophysiological follow up. In this study, subjects were performing the affect label task, the affect match task, the gender label task, and the shape map task just as we were seeing when their skin conductance response was being measured. Now, across this entire sample, affect labeling was found to be associated with smaller SCRs than effect matching.

And equivalent SCRs to shape matching control tasks. So, again here even in physiological arousal or in physiological responses you can see that affect labeling is linked with lowest or the least SCR or skin conducting responses and in that sense you can see that it is not only you know neurally suppressing the idea neurally suppressing the processing of affective information, but it also physiologically suppressing the processing of affective information. Interestingly gender labelling produces ah produce SCRs between the levels observed for the affect labelling and the affect matching you know target. tasks, but it was not significantly different from either. So, again this is sometimes there is a mediating sort of an effect which is very difficult to explain where that is really coming from. Again remember while they were doing the gender labeling they are also anyways some kind of spontaneous SPA is still happening there.

So, that might be the reason why the amygdala response or the SCR response actually in this case is slightly subdued or suppressed. Now one reason these latter effects that we

are just seeing in the psychophysiological follow up may not have been significant is that a number of subjects did not really show reliable SCRs in any of the conditions. So, it seems to be a property of the sample of participants that this experiment has recruited. which again it sort of dampens the statistical power of the entire sample as well and this may have occurred because face stimuli are not as emotionally provocative as let us say pictures derived from the international you know effective pictures database and so on. Now when the authors separated so they wanted to do some other analysis also and what they did was when they separated the sample into high and low neurotics you know neurotic population a clearer picture emerged.

So for non-neurotics who typically tend to be less reactive to negatively valenced stimuli they actually did not show any reliable SCR differences across any of the conditions. On the contrary those high in neuroticism actually produce stronger SCR responses to affect match and gender label trials and much weaker SCR responses to affect label and shape match trials. So in cases where this is actually happening where the participants have this natural tendency to have a higher amygdala response to higher effective response in that case you are actually seeing much weaker SCR responses in the affect labeling task which seems that this task is certainly recruiting you know symbolic processing of effect and by corollary also recruiting the RVL-PFC to overall dampen the phenomenal experience of negative effect. So, for those participants that were showing the SCR responses at all to emotional stimuli, the disruption hypothesis in that case were fully supported. So, this is again something that we can see that not only in fMRI studies or PET studies, but also in psychophysiological studies, we find support for the, you know, the disruption hypothesis which basically says that negative effect leads to, you know, some kind of symbolic processing of effect which recruits the RVL-PFC which basically does its job by down regulating the activity in the limbic regions which are typically involved in you know processing of affective information.

This is all for the current lecture. I will meet you with the next lecture where we will sort of look at some kind of clinical applications for the findings that we have reported so far. Thank you.